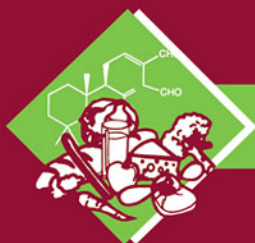


Dictionary of Nutraceuticals and Functional Foods

N. A. Michael Eskin
Snait Tamir



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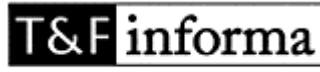
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Dedication

*This book is dedicated
to
a wonderful wife
Nella Eskin
and
a wonderful daughter
Orr Tamir*

Preface

The current emphasis in preventative medicine encourages healthy lifestyles such as a balanced diet and exercise. In recent years a balanced diet has focused on ensuring functional foods are part of our diet. Functional foods are similar in appearance to conventional foods, but in addition to providing basic nutritional components, have physiological benefits that can reduce the risk of chronic diseases. The bioactive components responsible for the health benefits of functional foods are referred to as nutraceuticals. The past decade has witnessed a dramatic expansion in research activities worldwide to identify new functional foods and nutraceuticals. The latter will hopefully enhance the health and wellbeing of an aging population.

Research on functional foods and nutraceuticals is scattered throughout the scientific literature with only a very few journals devoted specifically to nutraceuticals. We have attempted to bring together, in a concise and informative manner, some of the literature published on 480 functional foods and nutraceuticals. This dictionary, which is more of a mini-encyclopedia, provides the reader with useful information on the nature of the bioactives in functional foods and their reported efficacy in cell cultures, animal studies, and, in some cases, human clinical trials. In addition to providing the structures of some of the bioactives or nutraceuticals, data showing their efficacy are also included. The information is presented alphabetically with some areas more extensively researched in the literature than others. We hope this book will prove a useful resource for researchers, teachers, as well as those working in the functional food and nutraceutical industry by providing reliable and accurate information based solely on peer-reviewed literature.

The authors acknowledge the professional help afforded by the staff of Taylor & Francis as well as the assistance of Marie Speare, reference librarian at the University of Manitoba. The authors are particularly appreciative of the support given by their respective families and academic institutions in preparing this unique volume.

N.A.Michael Eskin
S.Tamir

The Authors

Michael Eskin, PH.D., was born and educated in Birmingham, England. He completed his B.Sc. Hons. degree in biochemistry and Ph.D. in physiological chemistry at Birmingham University where he conducted research on toxicology focusing on mercapturic acid formation.

After teaching at the Borough Polytechnic (now Southbank University) in London, England for several years he joined the Department of Human Nutritional Sciences (formerly the Department of Foods and Nutrition) at the University of Manitoba in Winnipeg, Canada where he served a term as vice-chair and chair. He is currently an associate dean of the Faculty of Human Ecology

Professor Eskin holds several patents and has published 15 chapters and 100 scientific papers related to edible oils, methodology and mustard gum. He has authored and edited 8 books including *Biochemistry of Foods* which was translated into German, Japanese and Malay. He is currently working on a third edition of this book. Dr. Eskin also coedited *Methods to Assess the Stability of Oils and Fat-Containing Foods*, published by the American Oil Chemists' Society, and more recently *Food Shelf Life Stability*, published by CRC Press and translated into Portuguese.

Professor Eskin was the recipient of a number of awards including the 2001 W.J.Eva Award for outstanding contributions to research and service by the Canadian Institute of Food Science and Technology. He was recently honored by the Natural Sciences and Engineering Research Council of Canada (NSERC) for holding an NSERC grant for more than 25 years.

Dr. Eskin is a Fellow of the Canadian Institute of Food Science and Technology and the Institute of Food Science and Technology in the UK. In 2004, he was inducted a Fellow of the American Oil Chemists' Society at their Annual Meeting in Cincinnati for outstanding contributions to the society and to oilseed research. He is an associate editor of the *Journal of the American Oil Chemists' Society* as well as sits on the editorial boards of *Food Chemistry* (UK), *Journal of Food Lipids* (USA), *Indian Journal of Food Science and Technology* and served a term on the board of Food Hydrocolloids (USA). He also sits on the advisory board of *INFORM*, the technical publication of the American Oil Chemists' Society.

Snait Tamir, Ph.D., is professor of biochemistry and nutrition sciences, and head of the Department of Nutrition Sciences at Tel Hai Academic College, Israel. In 1985 Dr. Tamir received her B.Sc. (cum laude), and in 1991 she received her Ph.D. (supervised by Prof. Yehudith Birk) in biochemistry and human nutrition from the Hebrew University of Jerusalem, Israel. In 1986 she completed her internship at Ichilov Medical Center in Tel Aviv, Israel and became a registered dietician. She conducted her postdoctoral study on "Nitric Oxide in DNA Damage and Repair" at the Division of Toxicology at the Massachusetts Institute of Technology, Cambridge, USA, with Professor Steven Tannenbaum, from 1992–1995.

In 1989, she studied, under the supervision of Professor T. Finlay, Medical Research Center, New York University, research techniques in breast cancer cells as part of a joint research project with Professor Yehudith Birk, the Hebrew University of Jerusalem.

In 1985 she was awarded The Dean's Scholarship at the Faculty of Agriculture Food and Environmental Sciences, The Hebrew University of Jerusalem. In 1987 she was awarded the Annual Distinction Award by the Women's Academic Association in Israel. She was also awarded the Rothschild Fellowship for the academic years 1992/3 by the Rothschild Foundation, Yad Hanadiv, Jerusalem, Israel, and the Guastella Fellowship for the academic years 1997/2000 by the Rashi Foundation, Jerusalem, Israel.

Dr. Tamir joined the academic staff at the Tel Hai Academic College in 1997 as a senior lecturer in the Department of Biotechnology and Environmental Sciences, in which she participated in the design, establishment, and management of the academic curriculum. Since 1999 she has served as head of the Nutrition Science Department and was head of the Biotechnology and Environmental Sciences Department in the years 2001–2002.

In 1999 Dr. Tamir joined the research group in the Laboratory of Natural Medicinal Compounds, Galilee Technological Center (MIGAL), which deals with the development of natural therapeutic compounds, mainly the isolation, characterization, and synthesis of new compounds, in collaboration with various leading academic institutes in Israel.

Dr. Tamir has published about 40 papers and book chapters. Her current research interest is the therapeutic actions of natural compounds such as phytoestrogens, antioxidants, whitening agents and psoriasis inhibitors. Based on the structure-activities relationship studies she aims to design the optimal anti-atherogenic compounds, hormone replacement agents, melanin biosynthesis inhibitors, and to develop new biological agents for psoriasis.

A

Acacia gum

Acacia gums, or gum arable, are Acacia-tree exudates that are highly branched galactan polymers with galactose or arabinose side chains terminated by rhamnose or glucuronic acid. It cannot be digested in the small intestine but behaves as a prebiotic by enhancing the growth of the probiotic bifidobacteria (Wyatt et al., 1986; Crociani et al., 1994). Michel and coworkers (1998) confirmed the similarity between two acacia gums and a prebiotic fructooligosaccharide with respect to their ability to decrease *Clostridium* sp. levels in human intestinal microbiota, as well as increase *Lactobacillus* sp. counts. However, the fructooligosaccharide preparation induced higher levels of *Lactobacillus* sp. The overall effect was attributed to increased production of short-chain fatty acids.

Hosobuchi et al. (1999) demonstrated the efficacy of supplementing diets with acacia gum, pectin, and guar gum for controlling hypercholesterolemia. A significant reduction was observed for both total and LDL cholesterol in 50 adults after four weeks on the supplemented diet.

Arabic gum was shown by Rehman et al. (2001) to scavenge nitric oxide. The decrease in the production of nitric oxide by arabic gum was later shown by Gamal el-adin et al. (2003) to protect against acetaminophen-induced hepatotoxicity in mice. This reduction in oxidative stress (nitric-oxide production) was similar to the protection by arabic gum against gentamycin-induced nephrotoxicity reported previously by Al-Majed et al. (2002).

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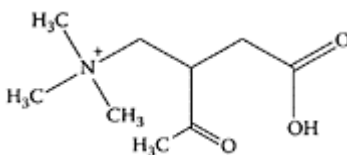
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Acetyl-L-carnitine

see also Carnitine

Acetyl-L-carnitine, an acetyl ester of carnitine, functions as a carrier of long-chain fatty acids into the mitochondria for β -oxidation. It also contributes to oxidative phosphorylation by the acetyl group forming acetyl-CoA, which enhances the supply of energy substrates to the Krebs's cycle (Dolezal and Tucek, 1981). During normal oxidative metabolism, the continuous production of reactive-oxygen metabolites (ROM) is extremely reactive, causing extensive mitochondrial DNA, cellular, and tissue damage over time. Such changes are associated with many chronic diseases, such as atherosclerosis, arthritis, autoimmune diseases, cancers, heart disease, and cerebrovascular accidents, as well as aging. Seidman and coworkers (2000) examined the ability of two mitochondrial metabolites, including acetyl-L-carnitine, to enhance mitochondrial function and reverse age-related processes in experimental rats. Acetyl-L-carnitine was found to delay the decline in mito-



Acetyl-L-carnitine. (From Bias et al., *Mitochondrion*. 4:163–168, 2004. With permission.)

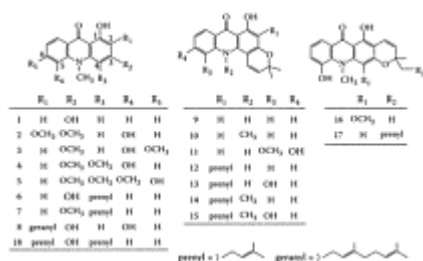
chondrial function by reducing age-associated deterioration in auditory sensitivity and improving cochlear function. Kopke and colleagues (2002) also found that acetyl-L-carnitine reduced noise-induced hearing loss in animals due to cochlear injury from oxidative stress. Turpeinen et al. (2000) showed acetyl-L-carnitine prevented loss of myocardial sympathetic nervous function in patients with diabetes. Kaur and coworkers (2001) demonstrated new antiaging effects of acetyl-L-carnitine by its ability to enhance glutathione S-transferase and multiple-unit activity and reduce lipid peroxidation and lipofuscin levels in the brain regions of aged rats. Biagiotti and Cavallini (2001) reported acetyl-L-carnitine was a far more effective and safer alternative to tamoxifen in the

treatment of Peyronie's disease. A recent study by Mazzio et al. (2003) showed acetyl-L-carnitine prevented neurological damage in mouse brain neuroblastoma cells by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP⁺), a cogent Parkinson-causing agent. This beneficial effect may be due to its ability to sustain neuronal energy supplies in the absence of oxygen or when there is a malfunction of mitochondrial oxygen utilization, typical of Parkinson's disease. Recent studies by Loots et al. (2004) suggested acetyl-L-carnitine may prevent MPTP⁺ toxicity by denying cation access to the inner mitochondrial membrane, thereby attenuating its ability to produce radical-oxygen species via the electron-transport chain. These results suggest acetyl-L-carnitine may have potential in the therapeutic treatment of Parkinson's disease.

Tomassini et al. (2003) found that acetyl-L-carnitine was well-tolerated as an alternative to the drug amantadine for the treatment of fatigue in multiple-sclerosis patients. A recent review by Ilias et al. (2004) pointed to the potential of acetyl-L-carnitine for treating complications associated with HIV infection and antiretroviral therapy. However, the data obtained so far were based on small, uncontrolled clinical trials and require further investigation.

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SCHEME A.1 Structures of acridone alkaloids tested for inhibition of TPA-induced EBV-EA activation. (From Itoigawa et al., *Cancer Lett.*, 193:133–138, 2003. With permission.)

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Acridone alkaloids

Acridone alkaloids have been isolated from a number of plant sources, including citrus plants (family *Rutacea*). Some of them have been shown to exhibit cytotoxic, antiviral, and antimalarial properties (Kawaii et al., 1999; Yamamoto et al., 1989; Queener et al., 1991). A screening test showed that acridone alkaloids from citrus plants exhibited the most potent inhibition of 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) activation (Takemura et al., 1995). Further studies by Itoigawa and coworkers (2003) isolated 17 acridone alkaloids from Rutaceous plants. Their structures are shown in Scheme A.1. Of these, the prenylated acridones were found to be the most potent cancer protective agents when tested in a short-term, *in vitro* assay of 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBVEA) activation in Raji cells. The prenylated acridone alkaloids included glycocitrin-II (6), *O*-methylglycocitrine-II (7), severifoline (12), and ataphyllinine (13). The importance of the prenyl group was confirmed with the synthetic diprenylated acridone, 1,3-dihydroxy-10-methyl-2,4-diprenylacridone (18). Using an *in vivo*, two-stage mouse skin carcinogenesis model, it reduced the percentage of tumor-bearing mice to 73 percent after 10 weeks (Figure A.1), and the number of papillomas by approximately 48 percent

after 20 weeks (Figure A.1B), compared to the nonprenylated acridones, 1,3-dihydroxy-10-methylacridone (1) and glycofilinine (5).

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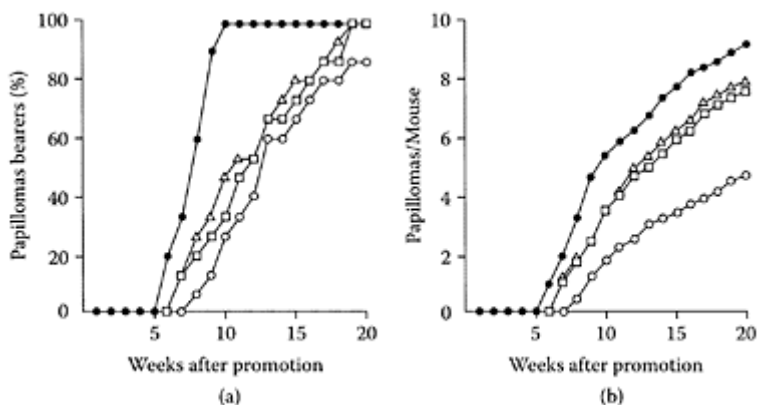


FIGURE A.1 Inhibitory effects of acridone alkaloids on DMBA-TPA mouse skin carcinogenesis. Tumor formation in all mice was initiated with DMBA (dimethylbenz[α] anthracene) (390 nmol) and promoted with TPA (1.7 nmol) twice weekly, starting one week after initiation, (a) Percentage of mice with papillomas. (b) Average number of papillomas per mouse: ●, control TPA alone; ○, TPA+85 nmol of 1,3-dihydroxy-10-methyl-2,4-diprenylacridone (18); △, TPA+85 nmol of 1,3-dihydroxy-10-methylacridone (1); □, TPA+85 nmol of glycofilinine (5). After 20 weeks of

promotion, a difference in the number of papillomas per mouse between the groups treated with acridones and the control was evident ($p<0.05$). (From Itoigawa et al., *Cancer Lett.*, 193:133–138, 2003. With permission.)

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Adlay

Adlay (*Coix lachryma-jobi* L.), a grass crop grown in China, is used as an herbal medicine and a food. A number of bioactive substances isolated from different parts of adlay were shown to exhibit anti-inflammatory, antitumor, and hypoglycemic activities. Early studies by Ukita and Tanimura (1961) and Tanimura (1961) showed the active component in adlay that inhibited the growth of Ehrlich ascites sarcoma was coixenolide. A number of benzoxazines isolated from adlay seeds were later found to have anti-inflammatory activity (Nagao et al., 1985). Chiang et al. (2000a) showed dehulled adlay had a significant effect on the growth of intestinal bacteria in rats. Animals fed adlay had normal, healthy walls with no pathogenic signs. In addition, there were higher concentrations of short-chain fatty acids in the GI tracts. One of these, butyric acid, was shown to inhibit the growth of colonic tumors (Smith and German, 1995). Kuo and coworkers (2001) found that methanolic extracts of adlay hulls exhibited multiple antioxidant properties and induced apoptosis in human histolytic lymphoma monocytic cells. The antitumor properties of adlay were further demonstrated by Chiang et al. (2000b) by its inhibition of sarcoma-180 tumors in mice. A methanolic extract of adlay was subsequently shown by Chang et al. (2003) to be antiproliferative on A549 lung cancer cells in mice by inducing cell cycle arrest and apoptosis. Shih et al. (2004) recently found that a diet containing 20 percent dehulled adlay suppressed the early events in the development of cancer and not the formation of tumors in azoxymethane-induced colon carcinogenesis in rats.

Kuo and coworkers (2002) identified the antioxidants in a 1-butanol extract of adlay hulls exhibiting strong, radical-scavenging activity as coniferyl alcohol, syringic acid, ferulic acid,

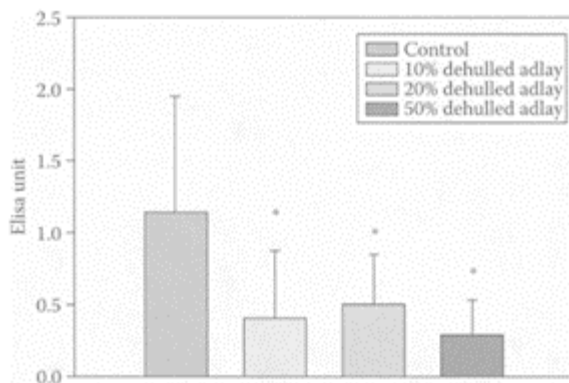


FIGURE A.2 Effects of different dosages of dehulled adlay on OVA-specific IgE levels in serum of mice consuming the test diets for six weeks and then intraperitoneally immunized with OVA plus alum. (From Hsu et al., *J. Agric. Food Chem.*, 51:3763–3769, 2003. With permission.)

syringaresinol, 4-ketopinoresinol, and a new lignan, mayuenolids. Hsu et al. (2003) showed that oral administration of several fractions obtained from dehulled adlay modulated Th1/Th2 cytokine production in cultured splenocytes obtained from ovalbumin (OVA)-immunized male BALB/c mice. This caused suppression of IgE biosynthesis (Figure A.2), which suggested it could be used to alleviate allergic symptoms.

A crude adlay-seed extract was shown by Kim and coworkers (2004) to exert hypolipidemic effects in obese rats maintained on a high-fat diet. The adlay extract modulated expression of both leptin and TNF- α , reducing body weight, food intake, fat size, adipose tissue mass, and serum hyperlipidemia. Adlay appears to have therapeutic potential for treating obesity.

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Adzuki beans

Adzuki beans (*Vigna angularis*), an important pulse crop in Asia, are particularly popular in Japan, China, and Korea. As a legume, its protein content and quality are high. A novel, antifungal peptide was recently isolated from adzuki beans by affinity chromatography and ion-exchange chromatography (Ye and Ng, 2002). The peptide, referred to as angularin, had a molecular weight of 8 kDa and was effective against fungal species, such as *Mycosphaerella arachidiicola* and *Botrytis cinerea*.

Three triterpenoid saponins were isolated from the hypocotyls of adzuki beans by Iida et al. (1999). Related compounds are known to scavenge superoxide radicals, as well as exhibit antioxidant and chelating activities (Yoshiki et al., 1995, 1996, 1997).

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Agrimony

Agrimony (*Agrimonia eupatoria*) is a valuable medicinal herb used mainly as a gastrointestinal tonic. It is characterized by long leaves with small, yellow flowers, one above the other in long spikes on a hairy, brown stalk, 2 to 3 feet high. A recent study by Gallagher and coworkers (2003) showed that compared to eight other plant sources, agrimony and avocado were the most effective in inhibiting the movement of glucose across a dialysis membrane. Previous research incorporating an aqueous extract of agrimony into the diet or drinking water of STZ-treated diabetic mice decreased weight loss, polydipsia, hyperphagia, and hyperglycemia (Swanston-Flatt et al., 1989; Gray and Flatt, 1998). This was accompanied by increased secretion of pancreatic insulin and insulin glucose uptake and metabolism *in vitro*. These studies suggest that the addition of agrimony as a dietary supplement could help to improve glycemic control in type 2 diabetic individuals.

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Ajoene

Ajoene (*E,Z*)-4,5,9-trithiadodeca-1,6,11-triene 9 oxide), an organic trisulphur compound originally isolated from garlic, is formed from the spontaneous degradation of alliin.



Ajoene. (From MacDonald and Langler, *Biochem. Biophys. Res. Comm.*, 273:421–424, 2000. With permission.)

The possible pharmacological role of garlic in the prevention and treatment of cancers was attributed to the presence of ajoene. Rendu and coworkers (1989) reported ajoene was the antiplatelet compound in garlic responsible for inhibiting platelet aggregation. Later work by Apitz et al. (1992) showed the antiplatelet activity of ajoene prevented thrombus formation induced by vascular damage. Urbina and coworkers (1993) also found ajoene to be a potent antiplatelet compound capable of inhibiting both epimastogotes and amastigotes of *Trypanoso-ma cruiz*, the causative agent for Chaga’s disease. Dirsch et al. (1998) reported ajoene-induced apoptosis in human promyleleukemic cells but not in peripheral mononuclear cells of healthy donors. The mechanism proposed was that ajoene stimulated peroxide formation in the leukemic cells and activated NF-κB. The antitumor properties of ajoene were demonstrated *in vivo* by Li et al. (2002ab, 2003), who showed it inhibited proliferation and induced apoptosis in several cancer-cell lines by activation of NF-κB and caspase-8. Hassan (2004) suggested that inhibition of proliferation and induction of apoptosis by ajoene was associated with blocking the G2/M phase of the cell cycle and activation of caspase-3 by ajoene, making it a new antileukemia agent for acute myeloid leukemia therapy (AML). Ajoene could be effective in elderly AML patients with poor tolerance to conventional chemotherapies. For example, Table A.1 shows the effect of ajoene with traditional drugs, cytarabine and fludarabine, on bcl-2 expression and caspase-3 activation in human-resistant myeloid leukemia cells. The most significant effect was activation of caspase-3, a prerequisite for apoptosis. A recent study by Ledezma et al. (2004) showed the cytotoxic effect of ajoene on murine melanoma B16F10 cells was also associated with activation of caspase-3 and subsequent apoptosis.

Using the water-maze test, Yamada et al. (2004) recently found that only Z-ajoene, and not alliin or diallyl disulfide, reduced acetylcholinesterase (AChE) activity in the brain of scopolamine-induced, memory-impaired mice. Excessive production of AChE leads to a deficiency of acetyl choline, resulting in a loss of memory and cognitive-impairment characteristic of Alzheimer’s disease. Improvements observed following treatments with Z-ajoene suggest it could be used to treat this disease.

Gallwitz and coworkers (1999) also showed that the antiparasitic and cytostatic properties of ajoene were due to its effect on key enzymes involved in antioxidant thiol metabolism. Ajoene was previously found to inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis, as well as in the later steps of the mevalonate pathway in rat hepatocytes and HepG2 cells (Gebhardt et al., 1994). In addition to being a precursor of cholesterol, mevalonate is also a precursor of other nonsteroid iso-prenoids (e.g., farnesyl and geranylgeranyl) that attach themselves to proteins and are crucial for cell proliferation (Grunler et al., 1994). Ferri and coworkers (2003) reported, for the first time, inhibition of protein prenylation and cell proliferation by ajoene in the smooth-muscle cells cultured from the aorta of Sprague-Dawley rats.

TABLE A.1

Bcl-2 Expression and Caspase-3 Activation in CD34+CD7+Human Resistant Myeloid Leukemia Cells Following Treatment with Cytarabine or Fludarabine in Presence or Absence of Ajoene

	Bcl-2 (U/million cells)			Activated caspase-3 (pg/million cells)		
	No ajoene	With ajoene	P	No ajoene	With ajoene	P
Control	227.7±15.0	212.9±14.	NS	51.4±5.0	97.8±9.0	NS
Cytarabine	24.8±3.0	4.1±0.3	<0.001	210.5±13.0	657.9±11.0	<0.001
Fludarabine	104.5±12.0	70.3±8.0	NS	183.7±10.0	265.9±16.0	NS

Source: From Hassan, *Leukemia Res.*, 28:667–671, 2004. With permission.

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Alcohol

see also Ethanol A considerable body of evidence associates moderate alcohol intake with a lower incidence of, and mortality from, coronary heart disease. Kannel and Ellison (1996) reviewed evidence of a protective effect due to alcohol raising HDL subfractions. A further discussion on the cardioprotective effects of alcohol by Gorinstein et al. (2002) suggested that, in addition to polyphenols, the antioxidant properties of ethanol can also prevent oxidation of LDL-cholesterol. This research further illustrates the importance of moderate alcohol consumption, as chronic alcohol consumption was shown to induce hepatic oxidation, leading to increased malondialdehyde levels in Wistar rats. Figure A.3 summarizes a study of 115 premenopausal, nonsmoking women conducted in four different regions in Europe. Bianchini et al. (2001) found an inverse correlation between alcohol consumption and 8-hydroxy-2'-deoxyguanosine (8-oxodGuo) lymphocyte levels (Figure A.3). The formation of 8-oxodGuo is a measure of oxidative damage to lymphocyte DNA. This unexpected finding pointed to the beneficial effects of moderate alcohol consumption. In a 12-year study of 38,077 males, Mukamal and coworkers (2003) confirmed the inverse relationship between alcohol consumption, at least three to

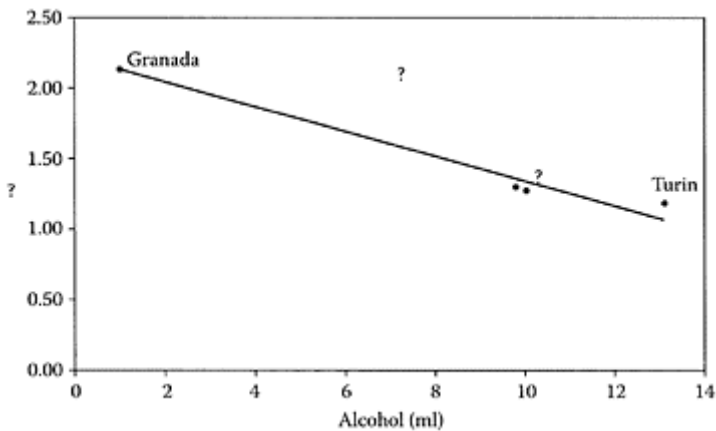


FIGURE A.3 Association between geometric mean 8-oxodGuo $\times 10^4$ levels and mean alcohol consumption among nonsmoking, premenopausal women between the four centers. (From

Bianchi et al., *Carcinogenesis*,
22:885–890, 2001. With permission.)

four days a week, and the risk of coronary heart disease.

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Alfalfa

Alfalfa (*Medicago sativa* L.) has been grown extensively as a livestock feed, while alfalfa sprouts are consumed as a garnish. It contains a large number of compounds, including saponins, flavonoids, tannins, coumestrol, carotenoids, and tocopherols. Flavonoids are known to have important health properties and include glycosides of apigenin, luteolin, and tricetin (Packer et al., 1999). In addition to five known apigenin and luteolin glycosides and adenosine, Stochmal and coworkers (2001a) identified four new apigenin glycosides and a luteolin glycoside in alfalfa not reported previously. Further work by Stochmal et al. (2001b) characterized 10 flavone glycosides, including six tricetin, one 3'-*O*-methyltricetin, and three chrysoeriol glycosides in the areal parts of alfalfa. Hwang et al. (2001) showed that pretreatment of soy and alfalfa extracts with acerola cherry extracts, a rich source of vitamin C, enhanced the antioxidant activity of soy and alfalfa extracts to inhibit LDL-oxidation (LDL⁺) (Figure A.4). The protective effect, only evident between alfalfa or soybean extracts and acerola cherry extracts, was attributed to synergistic interaction between its flavonoids and phytoestrogens with ascorbic acid in the cherry extract. In the case of alfalfa and acerola cherry extracts, this corresponded to 0.5 μ M genistein and daidzein, 0.1 μ M coumestrol and apigenin, and 102 μ M ascorbic acid.

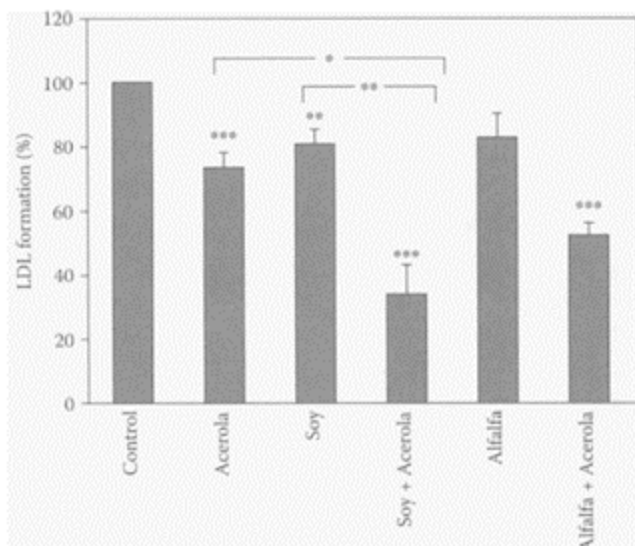


FIGURE A.4 LDL formation mediated by cells after addition of 100 µg/mL LDL protein. Cells were incubated under standard conditions (control) and preincubated with acerola, soy, soy and acerola, alfalfa, and alfalfa and acerola, extracts for five days, with male rabbit aortic endothelial cells. (From Hwang et al., *J. Agric. Food Chem.*, 49:308–314, 2001. With permission.)

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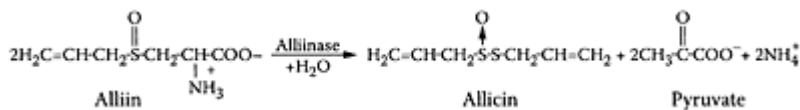
Allicin

Allicin (diallyl sulfonate) is one of the bioactive components of garlic (Rabinkov et al., 1994). It is formed in garlic by the action of the enzyme alliinase (alliin lyase, EC 4.4.1.4) on alliin [(+)*S*-2-propenyl L-cysteine *S*-oxide] (Scheme A.2). Eilat and coworkers (1995) showed allicin altered the serum lipids in hyperlipidemic rabbits. Elkayam et al. (2001) found a synthetic preparation of allicin reduced blood pressure in fructose-induced hyperinsulenemic, hyperlipidemic, hypertensive rats from a maximum of 153.4 mm Hg to 139.7 mm after 2 weeks. Allicin acted similarly to enalapril with respect to blood pressure, insulin, and triglycerides, suggesting it as a potential alternative treatment of blood pressure. Kang et al. (2001) showed allicin had immunomodulating activity, especially on macrophages. Inflammatory murine peritoneal macrophages treated with increasing levels of allicin induced tumoricidal activity in a dose-dependent manner (Figure A.5). This was accompanied by corresponding increases in the production of the tumor necrosis factor (TNF- α) and nitric oxide.

Further research was recommended to establish the mode of this modulation and to what degree it occurs *in vivo*.

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SCHEME A.2 Conversion of alliin to allicin by alliinase. (From Miron et al., *Anal. Biochem.*, 307:76–83, 2002. With permission.)

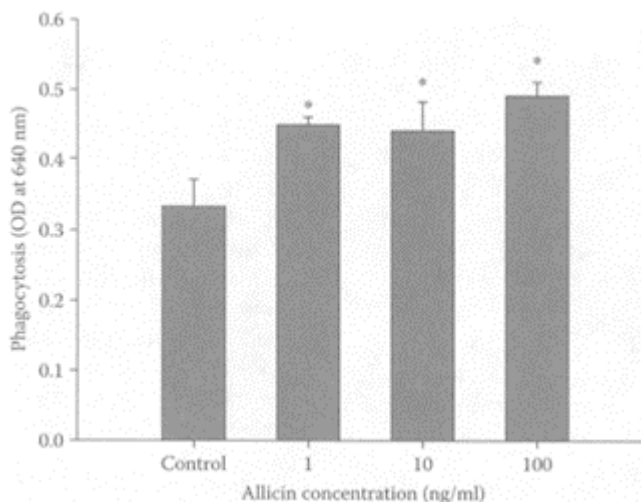


FIGURE A.5 Tumoricidal activities of allicin-treated murine peritoneal macrophages against a B16 melanoma-cell line. Results are the mean \pm S.E.M. of quintuplicates. Differences were significantly different at $*p<0.05$, and $**p<0.01$ from the control (no treatment). (Kang et al., *Nutr. Res.*, 21:617–626, 2001. With permission.)

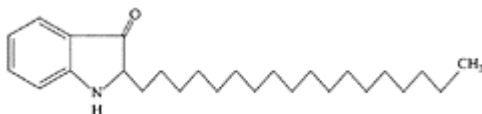
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Allium fistulosum

Allium fistulosum is a perennial herb grown around the world. However, most of the world's production is in China, Japan, and Korea. It is a member of the onion family and has been used in China to treat a wide range of diseases, including headache, abdominal pain, and diarrhea (Phay et al., 1999). Previous studies isolated a novel, antifungal compound in the roots of this herb, fistulosin.

Sang and coworkers (2002) isolated a new, unsaturated fatty-acid monoglyceride, glycerol mono-(E)-8,11,12-trihydroxy-9-octadecenoate, together with five compounds, tianshic acid, 4-(2-formyl-5-hydroxymethylpyrrol-1-yl) butyric



Fistulosin. (From Phay et al., *Phytochemistry*, 52:271- 274, 1999. With permission.)

acid, *p*-hydroxybenzoic acid, vanillic acid, and daucosterol. Some of these compounds are known to have bioactivity. The unsaturated fatty-acid monoglyceride and tianshic were both shown to inhibit the growth of *Phytophthora capsici*.

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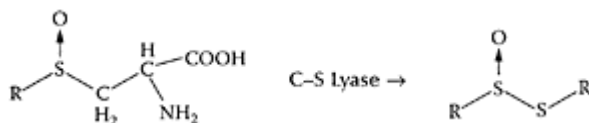
Allium thiosulfinates

see also Methylmethane thiosulfinate The juice from onions and garlic both inhibited platelet aggregation in human blood *in vitro* (Bordia, 1978; Srivastava, 1984; Goldman et al., 1995). The compounds responsible were formed by alliinase action on *S*-alk(en)yl-L-cysteine sulfoxides producing sulfenic acid, ammonia, and pyruvate, with the sulfenic acid then forming thiosulfinates. For example, *S*-propenyl-L-cysteine sulfoxide, the main sulfoxide in garlic, is converted to 1-propenylsulfenic acid (Scheme A.3), which oxidizes or cyclizes to form 1-propenyl-thiosulfinates (Block et al., 1992). Other sulfoxides in garlic and onion are also converted to thiosulfinates. Briggs and coworkers (2000) evaluated four thiosulfinate inhibitors of platelet aggregation. These included methyl methane

thiosulfinate, propyl propane-thiosulfinate, and 2-propenyl 2-propene-thiosulfinate (allicin), previously identified in freshly cut *Allium* vegetables, together with ethyl ethane-thiosulfinate, not previously identified. These researchers found propyl propane-thiosulfinate and allicin, at 0.4 mM, strongly inhibited antiplatelet activity by 90 percent and 89 percent, respectively. In comparison, ethyl ethane thiosulfinate and methyl methane thiosulfinate at the same concentration were somewhat weaker, inhibiting antiplatelet activity by 79 percent and 24 percent, respectively. Because the effects of the thiosulfinates were not additive, these researchers pointed out the difficulty of predicting the antiplatelet potential of *Allium* extracts based on their quantitation. Nevertheless, the ethyl ethane thiosulfinate, methyl methane thiosulfinate, and allicin proved far more potent platelet inhibitors compared to an equivalent concentration of aspirins.

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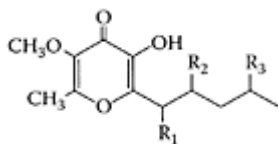
SCHEME A.3 Formation of thiosulfinate from S-propenyl-L-cysteine sulfoxide by cysteine sulfoxide lyase (C-S lyase) (where R and R'=propenyl, CH₃-CH=CH-). (Adapted from Xiao and Parkin, *J. Agric. Food Chem.*, 50:2488–2493, 2002.)

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Allixin

Allixin (6-methyl-2-pentyl-4H-pyran-4-one) is one of the organosulfur compounds found in aged garlic extract. Kodera and

coworkers (1989) identified this phenolic compound in garlic that had weak antimicrobial activity. Subsequent research by Nishino et al. (1990) showed allixin was an anticancer agent by inhibiting skin cancer in mice induced by 7,12-dimethylbenz[α]-anthracene (DMBA) and the promoter, 12-*O*-tetradecanoyl (TPA).



Allixin. (From Moriguchi et al., *Life Sci.*, 61:1413–1420, 1997. With permission.)

Allixin was also reported by Yamasaki et al. (1991) to inhibit aflatoxin B₁-induced mutagenesis in *Salmonella typhimurium*, as well as the formation of aflatoxin B₁DNA adducts. Moriguchi and coworkers (1997) examined the effect of allixin and its analogues on the survival and morphology of primary cultured neurons from fetal-rat brain. Allixin (1–100 ng/mL) significantly promoted the survival of neurons, as well as increased the number of branching points per axon in the hippocampal region. At higher concentrations (>1 microgram/mL), however, allixin was cytotoxic. Of the analogues examined, 2,6-dimethyl-3-hydroxy-4H-pyran-4-one (DHP) had potent neurotrophic activity at concentrations greater than 10 ng/mL without any cytotoxicity up to 10 microgram/mL. DHP was considered to be a useful prototype as a prophylactic drug for the treatment of neurodegenerative diseases. Allixin, a phytoalexin, is a stress compound produced by the plant when subjected to stress. Mahady and coworkers (2001) reported that allixin inhibited *Helicobacter pylori*. These researchers suggested reports that fresh garlic did not inhibit *H. pylori* growth were probably due to its absence of allixin, which is present only in stressed garlic.

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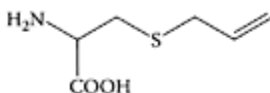
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S-Allyl-L-cysteine

S-Allyl-L-cysteine (SAC) is an organosulfur compound, which, together with allixin and its analogue, 2,6-dimethyl-3-hydroxy-4*H*-pyran-4-one (DHP), had antiaging,



S-Allyl-L-cysteine (SAC). (Adapted from Arnault et al., *J. Pharm. Biomed. Anal.*, 37:963–970, 2005.)

learning and memory improvement, neurotrophic effects, and antioxidant activity associated with aged garlic extract (Yamasaki et al., 1994; Moriguchi et al., 1996, 1997; Nishiyama et al., 1997). Ito and coworkers (2003) showed SAC exerted a protective effect on amyloid β -protein-induced cell death in nerve growth, factor-differentiated PC 12 cells, a model of neuronal cells. Amyloid β -protein ($A\beta$), a 40–43 amino acid peptide, is involved with the formation of senile plaques in the brains of Alzheimer patients, as well as being cytotoxic to cultured neurons (Yao et al., 1999; Ekinci et al., 2000). SAC selectively protected neurons from $A\beta$ -induced neurotoxicity. Kim and coworkers (2001) reported it was the antioxidant activity of garlic extract and SAC that differentially regulated nitric oxide in a murine macrophage by inhibiting iNOS expression and NF- κ B activation while increasing nitric oxide in epithelial cells. This selectivity in regulation by garlic extract and SAC may contribute to their antiinflammatory effect and ability to prevent atherosclerosis.

The ability of SAC to prevent gentamicin renal damage was attributed by Maldonado et al. (2003) to its antioxidant properties. SAC reduced oxidative stress through preservation of Mn-SOD, glutathione peroxidase, and glutathione reductase activities.

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Almonds (*Prunus amygdalus*)

Almonds, popular tree nuts worldwide, are used in snack foods and as ingredients in bakery and confectionery products. Fraser (1999) pointed out that substituting almonds or walnuts for traditional fats in the human diet reduced LDL cholesterol by 8–12 percent. Eating nuts is frequently associated with a substantial decrease in the risk of coronary heart disease of between 30–50 percent. In addition to their ability to reduce cholesterol, almonds have been reported to exhibit anticancer properties. Jenkins et al. (2002) compared whole almonds as a snack to low-saturated, whole-wheat muffins in a randomized, crossover study involving 27 men and women who consumed three isoenergetic supplements each for one month. The supplements contributed 22.2 percent of energy and were either fulldose almonds (73±3 g/d), half-dose of

TABLE A.2

Effect of Almonds on Blood Lipids of Hyperlipidemic Subjects¹

Control		Almonds			
		Half-dose		Full-dose	
Week 0	Treatment ²	Week 0	Treatment ²	Week 0	Treatment ²

Cholesterol, mmol/L

Total	6.45 ±0.1	6.44±0.1 5	6.47±0.1	6.25±0.15	6.60±0.1	6.21±0.15
LDL	4.34±0.1	4.22±0.1 3	4.30±0.1	4.10±0.12	4.45±0.1	4.01±0.12
HDL	1.43±0.0	1.14±0.08	1.38±0.0	1.43±0.08	1.40±0.0	1.45±0.09
Ratios						
Total: HDL Choi.	4.95±0.2	4.89±0.24	5.07±0.2	4.68±0.24	5.00±0.2	4.58±0.23
LDL: HDL Choi.	3.32±0.0	3.23±0.18	3.40±0.2	3.11±0.20	3.40±0.1	2.99±0.19
Cholesterol						
Oxidized LDL						
Conjugated dienes	64±3	60±2	65±3	53±3	62±3	51±2
Conjugated dienes/LDL	14.8±0.6	14.3±0.5	15.3±0.8	13.4±0.6	14.1±0.6	12.9±0.03

¹Values are mean±SEM. N=27.

²Treatment values represent the mean of weeks 2 and 4.

Source: Adapted from Jenkins et al., *Circulation*, 106:1327–1332, 2002.

almonds plus half-dose muffin, or a full-dose muffin. Significant changes in serum lipids were observed for almonds, which are summarized in Table A.2. Both half- and full-dose almonds significantly reduced LDL cholesterol and LDL: HDL cholesterol, while only full-dose almonds significantly affected lipoprotein and oxidized LDL levels. A linear response to almonds was observed, which suggested that for each 7-g portion of almonds, there was a 1 percent reduction in LDL cholesterol. It was apparent from this study, together with epidemiological data, that the consumption of almonds may reduce the risk of coronary heart disease.

Davis and Iwahashi (2001) showed wholealmond consumption significantly reduced aberrant crypt foci compared to wheat bran and cellulose, suggesting a possible reduction in colon-cancer risk. Takeoka and coworkers (2000) identified three triterpenoids in the hulls of almonds, including betulinic, oleanolic, and ursolic acids. Sang and coworkers (2001) isolated a new, prenylated benzoic acid, together with catechin, procatechuic, and ursolic acids, in almond hulls. Many of these triterpenoids have been shown previously to have anti-inflammation, anti-HIV, and anticancer activities, suggesting almond hulls are rich sources of these bioactive compounds. Pinelo et al. (2004) recently showed almond-hull extracts had almost 60 percent higher antioxidant capacity compared to pine sawdust, in spite of being much lower in phenolic compounds.

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Aloe vera

Aloe vera, a member of the *Liliaceae* family, is a tropical plant originating in the warm, dry climates of Africa. Of more than 360 *Aloe* species recognized, *Aloe barba-densis* Miller is the main commercial one used for its medicinal properties. Corsi and coworkers (1998) reported that *Aloe vera* had therapeutic potential by reducing the growth in pleural tumor-bearing rats. Shamaan et al. (1998) also found that vitamin C and *Aloe vera* both reduced the severity of chemical hepatocarcinogenesis in rats. An *Aloe vera* gel was found to contain small-molecular-weight immunomodulators, G1C2F1, capable of restoring ultraviolet B (UVB)-suppressed accessory-cell function of epidermal Langerhans cells (LC) *in vivo*. Lee and coworkers (1999) showed that topical application of G1C2F1 to the abdominal skin of mice reduced the suppression of contact sensitization exposed to UVB radiation. *Aloe vera* enhanced wound healing by increasing the levels of type III collagen in dermal wounds in rats (Chithra et al., 1998). Extracts of *Aloe vera* were found to exert anti-inflammatory activity by inhibiting cyclooxygenase (Vasquez et al., 1996). Avila and coworkers (1997), however, pointed out that *Aloe vera* gels contain cytotoxic, low-molecular-weight compounds, which must be removed or reduced in commercially prepared products. Pugh et al. (2001) identified a high-molecular-weight immunostimulatory polysaccharide from commercial *Aloe vera* juice, aloeride, containing glucose (37.2 percent), galactose (23.9 percent), mannose (19.5 percent), and arabinose (10.3 percent). While aloeride only accounted for 0.015 percent of the crude juice, it exhibited very potent immunostimulatory activity compared to the main carbohydrate component, acemannan. Aloeride as an immunostimulant could be beneficial for wound healing and immunotherapy.

A supercritical carbon dioxide extract from *Aloe vera* skin was shown by Hu et al. (2004) to be a superior antioxidant to BHT or α -tocopherol. A quality and safety (HACCP) management system was recently developed by He et al. (2005) for processing *Aloe vera* gel juice for the food industry.

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TABLE A.3

Total Cholesterol, LDL Cholesterol, HDL Cholesterol, and VLDL Cholesterol levels (mg/dL) of Hypercholesterolemic Rabbits

Lipid parameters	Diet					
	Control		Amaranth oil		Extruded amaranth	
	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21
Total Cholesterol	201±29.6	173±38.8	219±27.1	179±27.6	196±23.7	97.3±20
LDL Cholesterol	159±26.2	148±36.6	183±27.5	145±26.7	162±20.9	72.8±20.8
HDL Cholesterol	34±4.01	15.4±1.75	28.3±1.45	20.8±4.10	31.3±4.33	18.1±1.37
VLDL Cholesterol	8.23±1.06	9.63±1.02	7.32±1.27	4.08±0.39	8.28±1.94	4.52±0.72

Source: Adapted from Plate and Areas , *Food Chem.*, 76:1–6, 2002.

Amaranth

Amaranth, a seed native to South America, has a protein content ranging from 14–18 percent and an excellent balance of amino acids. In addition, amaranth contains

tocotrienols and squalene, both of which affect cholesterol biosynthesis. Chaturvedi and coworkers (1993) reported that amaranth seeds exerted a hypocholesterolemic effect in male Wistar albino rats compared to Bengal gram. Qureshi et al. (1996) found that serum total cholesterol and LDL cholesterol were 10–30 percent and 7–70 percent lower, respectively, in female chicks fed amaranth-containing diets. Grajeta et al. (1999) reported that the addition of sunflower oil augmented the hypolipidemic effect of amaranth. The hypocholesterolemic effect of extruded amaranth was reported by Plate and Areas (2002). A reduction in total cholesterol and LDL cholesterol occurred in hypercholesterolemic rabbits fed extruded amaranth for 21 days compared to the control and amaranth oil diets (Table A.3). VLDL levels were approximately 50 percent lower in rabbits fed either the extruded amaranth or amaranth oil diet compared to the control. Ethanolic extracts from two amaranth species were found by Klimczak and coworkers (2002) to exhibit strong antioxidant activity in a β -carotenelinoleic acid model system. Total phenolic content ranged from 39.17 to 56.22 mg/100 g for *Amaranthus caudatus* and *Amaranthus paniculatus* seeds, respectively. Berger et al. (2003) showed a diet containing amaranth flakes (*Amaranthus cruentus*) decreased total cholesterol by 10 percent, but HDL and total cholesterol/HDL ratio remained unchanged. These researchers suggested that not all amaranth species have cholesterol-lowering properties, although they are still excellent sources of nutrients.

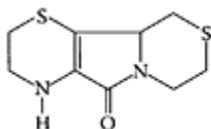
Tosi et al. (2001) obtained a high-fiber product from amaranth grain by differential milling. Using pneumatic classification, it was possible to obtain a high-fiber product that contained 63.9 percent insoluble fiber.

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Aminoethylcysteine ketimine

Aminoethyl-cysteine ketimine is a natural, sulfur-containing, tricyclic member found in a variety of vegetables, including garlic, spinach, tomatoes, asparagus, aubergine, onion, pepper, and courgette (Macone et al., 2002). It is an antioxidant-protecting submitochondrial particle from lipid peroxidation (Pecci et al., 1995). The direct health benefits from aminoethylcysteine ketimine, however, remain to be determined.



Aminoethyl cysteine ketimine. (Adapted from Macone et al., *J. Agric. Food Chem.*, 50:2169–2172, 2002.)

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Angelica

Angelica is a popular herb in North America, similar to the Chinese herb “Dong Quai.” The most common use for angelica recommended by herbalists is as an “emmanagoga” agent to promote menstrual flow and regulate menstrual cycles. However, it contains compounds that are extremely carcinogenic to experimental animals. Fujioka et al. (1999) found a chloroform extract from the roots of *Angelica japonica* strongly inhibited human gastric adenocarcinoma. Several compounds, in addition to caffeic acid methyl ester, were identified, including a new furanocoumarin, named japoangelone, together with four furanocoumarin ethers and four polyacetylenic compounds. Furimi et al. (1998) found that a number of falcariindiol furanocoumarins exhibited antiproliferative activity using the MTT assay. Matsuda and coworkers (1998) previously showed that a methanolic extract from the roots of *Angelica furcijuga* protected the liver against injury induced by D-galactosamine (D-GaIN) and lipopolysaccharide (LPS). A comparison of

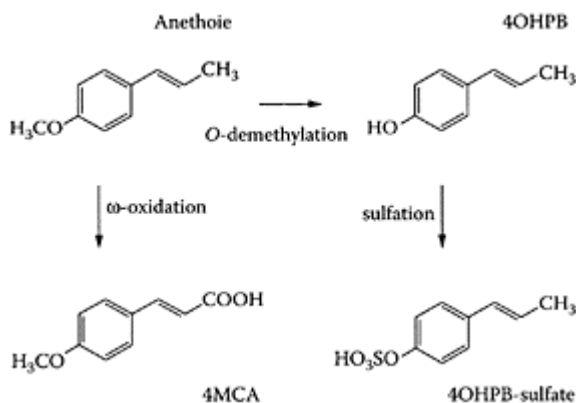
the inhibitory activities of acetylated khellactones with coumarins found acyl groups were essential for potent activity. A polysaccharide, angelan, purified from the oriental herb *Angelica gigas* Nakai, was reported by Han et al. (1998) to stimulate immune function.

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Anise

Anise (*Pimpinella anisum* L.), an annual herb with white flowers and small green-to-yellow seeds, is grown on a commercial scale in Southern Russia, Bulgaria, Malta, Spain,



SCHEME A.4 Proposed metabolism of anethole in rat hepatocytes. (From

Nakagawa and Suzuki, *Biochem. Pharmacol.*, 66:63–73, 2003. With permission.)

Italy, North Africa, and Greece. It is grown for its fruits, commercially called seeds, which are used for flavoring. The fruit yields a syrupy, fragrant, volatile oil that accounts for 2.5–3.5 percent of the fruit. The major aromatic component in the oil is an alkylbenzene, anethole, which comprises around 90 percent of the oil. Anethole [1-methoxy-4-(1-propenyl) benzene] has been shown to exhibit both antimicrobial and antimutagenic activities (Rompelberg et al., 1993; Curtis et al., 1996). The *trans* isomer of anethole is the most abundant form, accounting for around 99 percent (Toth, 1967). Chainy et al. (2000) showed anethole suppressed TNF-induced lipid peroxidation and the generation of reactive oxygen (RO), which probably explains its ability to suppress inflammation and carcinogenesis. Elgayyar et al. (2001) found anise oil was highly inhibitory to molds. The total antioxidant activity of water and ethanol extracts obtained from anise seeds, using a linoleic-acid emulsion, was recently shown to be much stronger than α -tocopherol (Gulcin et al., 2003). Nakagawa and Suzuki (2003) examined the metabolism of *trans*-anethole and its metabolites using freshly isolated rat hepatocytes and cultured MCF-7 human breast-cancer cells. Anethole was rapidly converted into at least three metabolites, 4-methoxycinnamic acid (4MCA), 4-hydroxy-1-propenylbenzene (4OHPB), and the monosulfate conjugate of 4OHPB, as shown in Scheme A.4.

The hydroxylated intermediate, 4OHPB, rather than the parent molecule appeared to be responsible for inducing cytotoxic effects in the liver and estrogenic-like effects in MCF-7 cells.

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Anka

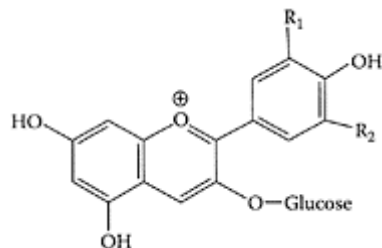
Anka (or Red Mold Rice; Red rice), a fermented rice product with *Monascus* sp., is very popular in Asia. It has been used for more than 100 years in Chinese medicine to assist digestion and blood circulation. A number of secondary metabolites produced by *Monascus ruber* are mevilonin and lovastatin, monoacolin capable of inhibiting the rate-limiting enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl CoA reductase (Endo and Monoacotin, 1980). The hypocholesterolemic potential of these compounds was reported in mammalian species, including humans (Endo, 1985). Wang and coworkers (2000) fed a high-fructose (30 percent) diet containing dried Anka powder (2 percent) to experimental rats with hypertriglyceridemia. After six months, the levels of serum triacylglycerols, total cholesterol, VLDL-cholesterol, and LDL-cholesterol all decreased significantly, while HDL cholesterol increased significantly compared to the 30 percent fructose diet. This study showed Anka was capable of suppressing hypertriglyceridemia and hyperlipidemia in rats and has the potential to do the same for humans.

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Anthocyanins

Anthocyanins are primarily responsible for the colors of fruits, fruit juices, wines, flowers, and vegetables. They are a subgroup within the flavonoids characterized by a



R₁

R₂

Anthocyanin

H	H	Pelargonidin-3-glucoside
OH	H	Cyanidin-3-glucoside
OH	OH	Delphinidin-3-glucoside
OCH ₃	H	Peonidin-3-glucoside
OCH ₃	OH	Petunidin-3-glucoside
OCH ₃	OCH ₃	Malvidin-3-glucoside

SCHEME A.5 Anthocyanin skeleton.
(From Clifford, *J. Sci. Food Agric.*,
50:1063–1070, 2000. With
permission.)

C-6-C-3-C-6 skeleton attached to a sugar (Scheme A.5). The six major anthocyanin aglycones or anthocyanidins are pelargonidin, cyanidin, delphinidin, peonidin, petunidin, and malvidin (Mazza and Miniati, 1993). These pigments have been reported to have a number of health benefits, particularly their antioxidant activity (Lapidot et al., 1999; Pratt, 1992; Wang et al., 1999). The low incidence of cardiovascular disease found in certain parts of France, known as the “French Paradox,” was attributed to consumption of red wine, which contains substantial amounts of flavonoids, mostly anthocyanins, as high as 3200 mg/L (Lapidot et al., 1999). Seeram and Nair (2002) conducted the first study evaluating anthocyanidins, as well as several anthocyanins using a liposomal model system with antioxidant activities measured by their ability to inhibit the fluorescence intensity decay of an extrinsic probe, 3-[-(6-phenyl)-1,3,5-hexatrienyl]phenyl-propionic acid, caused by free radicals generated during metal ion-induced peroxidation. Antioxidant activity increased with increasing number of hydroxyl groups on the B ring of the anthocyanidin, while methoxyl groups diminished the antioxidant activity. Anthocyanidins with a hydroxyl group at three position exhibited potent antioxidant activity. Substitution at position three

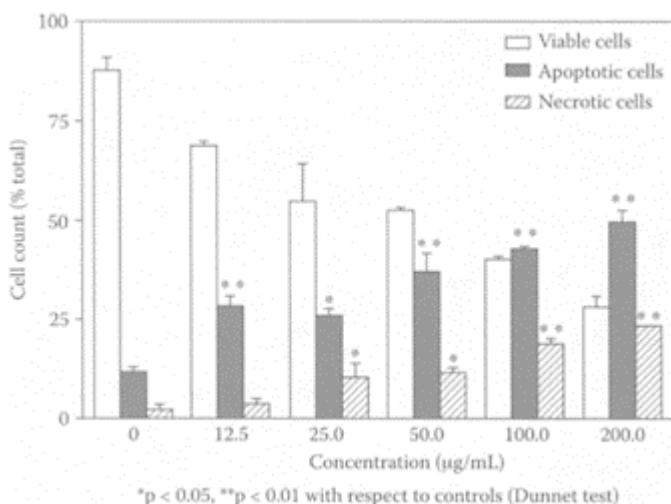


FIGURE A.6 Fraction of viable, apoptotic, and necrotic cells, as detected in Jurkat cells treated with cyanidin-3-*O*-β-glucopyranoside at doses ranging from 12.5–200 μg/mL for 24 h. Cells were removed from treated and untreated cultures and stained with bannexin V flourescein isothiocyanate and propidium iodide. The presented is averaged from three independent experiments, with error bars denoting standard errors. (Fimognari et al., *Biochem. Pharmacol.*, 67:2047–2056, 2004. With permission.)

in the C ring also had a major effect on the antioxidant activity of anthocyanidins. Espin and coworkers (2000) found anthocyanin-based fruit extracts exhibited radical-scavenging capacity (RSC) using the 2,2-diphenyl-1-picryl-hydrazyl radical (DPPH•). Of the fruits examined, black chokeberry and blackthorn were the most active, while strawberry and elderberry were the least active.

Lazze and coworkers (2004) examined the effects of two aglycone anthocyanins, delphinidin and cyanidin, on cell-cycle progression and induction of apoptosis in human uterine carcinoma and colon adenocarcinoma cells and in normal human fibroblasts. Over the concentration range of 100–200 μM, cyanidin interfered with the cell cycle of normal cells, which contrasted with delphinidin's inhibition of cell proliferation in both normal

human fibroblasts and pro-apoptotic activity in cancer cells. The greater effect associated with delphinidin was attributed to the presence of three hydroxyl groups on the B ring, which may be important for biological activity.

Fimognari et al. (2004) showed that cyanidin-3-*O*- β -glucopyranoside, an anthocyanin found in pigmented orange juice, induced apoptosis in two human leukemia cell lines, Jurkat T and HL-60 promyelocytic cells. For example, treatment of Jurkat cells with this anthocyanin, even at the lowest level tested (12.5 μ g/mL), increased apoptotic cells (Figure A.6). The potential of cyanidin-3-*O*- β -glucopyranoside, as a chemopreventive or chemotherapeutic agent, requires further study. To be effective, such compounds must be bioavailable; however, anthocyanins, like many other nutraceuticals, are very poorly absorbed. Netzel et al. (2001) reported that following ingestion of 153 mg of anthocyanins by healthy volunteers, only 0.02 to 0.05 percent was detected in the urine. A review of the functional properties and health-related properties of anthocyanins was recently published by Stinzing and Carle (2004).

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Antioxidants

see also Vitamins A, C, E, and K In addition to the natural antioxidant vitamins A, C, and E, there are a multitude of phenolic compounds that are responsible for the potent antioxidant properties of fruits, vegetables, and herbs. More than 200 epidemiological studies pointed to a strong association between the low consumption of fruits and vegetables and incidence of cancer (Willett and Trichopoulos, 1996). This association was attributed to the presence of antioxidants that protect cells from reactive-oxygen species that lead to DNA damage, mutation, and, ultimately, carcinogenesis (Boone et al., 1997). Thus, an increase in the consumption of some antioxidants can actually reduce oxidative damage and the development of some cancers. More recent data, however, suggests that reactive-oxygen species are used by cells in the signaling process that activates programmed cell death, or apoptosis, to eliminate cancer cells. Thus, inhibition of apoptosis by antioxidants may interfere with the elimination of precancerous or cancerous cells and actually promote cancers in individuals at risk for carcinogenic lesions. A review by Lopaczynski and Zeisel (2001) questioned whether cancer patients should be given dietary supplements containing much higher levels of antioxidants compared to a regular diet. This could explain why vitamin E and β -carotene enhanced lung cancer in heavy smokers, while protecting against prostate cancer (Heinonen et al., 1998). Further confirmation was provided by Wenzel et al. (2004) who showed that, while antioxidant vitamins, such as ascorbic acid, may play a role in cancer prevention, they could have different effects at different stages in the carcinogenic process. Using HT-29 human colon carcinoma cells, Wenzel and coworkers (2004) demonstrated the ability of ascorbic acid to interfere with apoptosis induced by the antitumor drug camptothecin or the flavonoid flavone. A significant increase in mitochondrial reactive-oxygen species (superoxide anion) by camptothecin and the flavone normally precedes down-regulation of bcl-X_L and apoptosis. This was prevented by the presence of 1 mM ascorbic acid, which reduced the amount of superoxide anion to that found in the control cells (Figure A.7). These results also raised concern regarding the high intake of antioxidant vitamins during chemotherapy.

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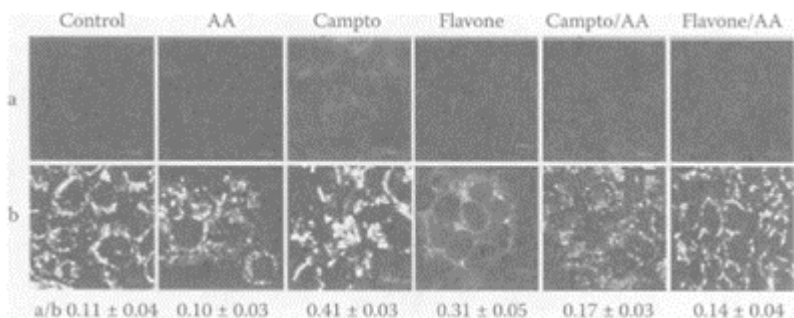
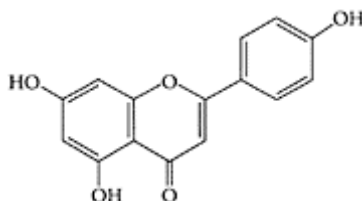


FIGURE A.7 Ascorbic acid prevents the appearance of mitochondrial O_2 . Cells were incubated with medium alone (control), or with 1 mM ascorbic acid (AA), or with 50 μ M camptothecin (campto), or 150 μ M flavone in the absence or presence of 1 mM ascorbic acid for 6 h. During the last period of incubation, cells were loaded with proxyfluorescamine for the detection of O_2 (a) in combination with MitoTracker for the visualization of mitochondria (b). The fluorescence ratios of a \over b were determined for the mitochondrial areas only. (Wenzel et al., *Carcinogenesis*, 25:703–712, 2004. With permission.)

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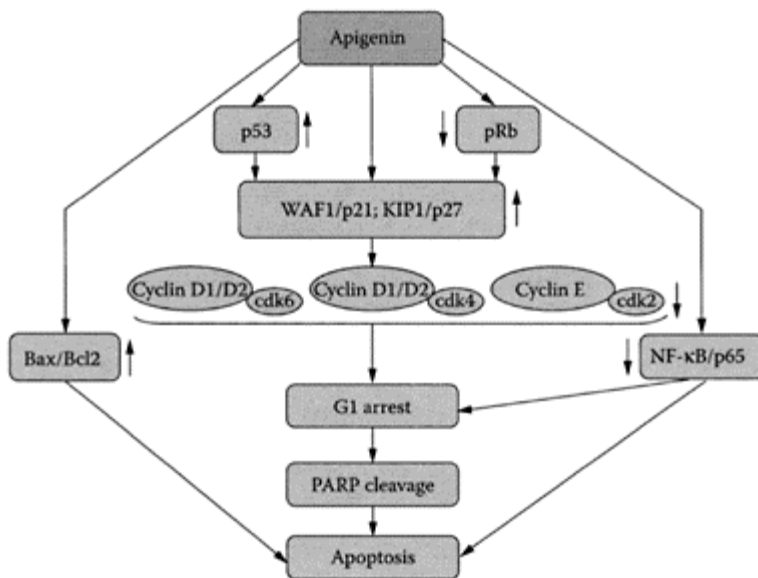
Apigenin

Apigenin, a flavonoid compound, is the major constituent of the herb chamomile. It is a 4',5,7-trihydroxyflavone, which appears to have a variety of medicinal uses, including the treatment of HIV, inflammatory-bowel disease, and skin conditions. It is also found in quite a number of other plant sources, including parsley, onions, tea, orange, wheat sprouts, and some seasonings (Birt et al., 1998; Duthie and Crozier, 2000). Chamomile flower is licensed in Germany as a medicinal tea, a rinse or gargle, cream, ointment, and vapor-inhalant bath additive. Apigenin



Apigenin. (From Zheng et al., *Life Sci.*, 76:1367–1379, 2005. With permission.)

was shown to inhibit tetradecanoyl-phorbol-13-acetate-(TBA)-mediated tumor promotion in mouse skin. Kavutcu and Melzig (1999) examined a number of flavonoids and found apigenin inhibited 5'-nucleotidase (5'-ribonucleotide phosphohydrolase, 5'-NT) activity, which could explain its pharmacological effects. Morton and Griffiths (1999) suggested a possible relationship between flavonoids, such as apigenin, and the prevention of prostate disease. Gupta et al. (2001) showed that apigenin caused selective cell-cycle arrest and apoptosis of several human prostate carcinoma cells but did not affect normal cells. An in-depth investigation by Gupta and coworkers (2002) showed apigenin inhibited serum- and androgen-stimulated, prostatespecific antigen (PSA) protein levels in human prostate carcinoma LNCaP cells concomitant with cell growth inhibition *via* G1-phase arrest and apoptosis. Based on this research, the following model was proposed (Scheme A.6), which confirms the potential of apigenin for the



SCHEME A.6 Proposed model for apigenin-mediated cell dysregulation and apoptosis of human prostate carcinoma LNCaP cells. (From Gupta et al., *Oncogene*, 21:3727–3778, 2002.)

treatment of prostate cancer. A recent study by Zheng and coworkers (2005) also found apigenin had considerable potential for the treatment of cervical cancer by inducing p53 expression in human cervical carcinoma cells (HeLa), which resulted in cell-cycle arrest and apoptosis.

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Apple

Fruits, like vegetables, are known to have healthy properties. In fact it has been shown that the peels of fruit are among the major sources of antioxidants (Bocco et al., 1998; Gorinstein et al., 1998). An international study involving Israel, Spain, Poland, the Czech Republic, and Korea (Leontowicz and coworkers, 2002) examined the bioactive compounds in apples, peaches, and pears and their influence on lipids and antioxidant capacity in rats. The total polyphenols were almost three times higher in apple fruit and peels compared to the other fruit. Caffeic acid, *p*-coumaric, and ferulic acids, as well as the total radical-trapping antioxidative potential (TRAP), were also significantly higher in apple fruit and peels. No differences in dietary fiber were observed among the fruits examined. This study showed apples had the highest content of biologically active compounds, making them the preferred source for the dietary prevention of atherosclerosis. Knekt and coworkers (2000), in a large study involving 9,208 Finnish men and women 15 years and above, found a strong association between intake of apples and decreased risk of thrombotic stroke. A later study by Young and coworkers (2002) showed that a low-antioxidant diet supplemented with 10 percent apple/ broccoli mixture fed to a chicken model stabilized erythrocytes, as well as reduced oxidation of muscle proteins and lipids in cooked liver. A number of *in vitro* studies attributed the ability of apple extracts to inhibit proliferation of tumor cells to the presence of phenolic/flavonoid antioxidants. Lapidot and coworkers (2002) cautioned that these results may be misleading, as the inhibition may be indirectly caused by hydrogen peroxide generated from interaction between the phenolics and the cell culture media. Consequently, the effects attributed to flavonoids and phenolics may be the result of the artifact production of oxidative stress. These researchers suggested that either catalase or metmyoglobin in the presence of a reducing agent be used to decompose any hydrogen peroxide formed so as to prevent such artifacts from occurring.

The high antioxidant capacity of apple polyphenols observed *in vitro* could not be found by Lotito and Frei (2004a) *in vivo*. No significant increase in resistance to oxidation was observed in the plasma of six healthy subjects up to four hours after eating five apples. This suggested poor absorption and metabolic conversion of apple polyphenols, as previously observed for the consumption of black tea (Cherubini et al., 1999). A follow-up study by Lotito and Frei (2004b) showed that it was urate, not flavonoids, responsible for the increased plasma antioxidant activity following apple consumption. They suggested that the antioxidant health effects attributed to flavonoids in fruit may be confounded by the metabolic effect of fructose on urate. Increase in

plasma urate had been reported previously in healthy individuals following consumption of tea (Natella et al., 2002) and red wine (Day and Stansbie, 1995).

Using a modified total-oxylradical scavenging (TOSC) assay, Wolfe et al. (2003) found the total antioxidant activity in the peels from four different apple varieties (Rome Beauty, Idared, Cortland, and Golden Delicious) were significantly ($p<0.05$) higher compared to the flesh and flesh+peel. Based on the effective median dose (EC_{50}), they also showed, for the first time, that apple peels exhibited greater antiproliferative activity against HepG₂ human liver-cancer cells than did the corresponding flesh or flesh +peels (Table A.4). The low EC_{50} for Rome Beauty flesh and peel suggested synergism between the phytochemicals in the flesh and peel, as there was no measurable inhibition with the flesh alone. Antiproliferative activity on human liver-cancer cells had been reported previously by Liu and coworkers (2001) using extracts from Fuji, Gala, and Red Delicious apples.

TABLE A.4

^a EC_{50} Values for Inhibition of HepG₂ Human Liver-Cancer Cell Proliferation by Phytochemical Extracts of Apples (Mean+SD, $n=3$)

Apple	Flesh (mg/mL)	Flesh+Peel (mg/mL)	Peel (mg/mL)
Rome Beauty	a	26.5+0.3	12.4+0.4
Idared	a	125.1+58.8	16.6+0.2
Cortland	103.9+16.5	74.1+4.0	15.7+0.3
Golden Delicious	155.3+11.7	107.7+22.7	20.2+0.7

^aThe EC_{50} value could not be calculated from the dose-response curve.

Source: From Wolfe et al., *J. Agric. Food Chem.*, 50:5058–5062, 2003. With permission.

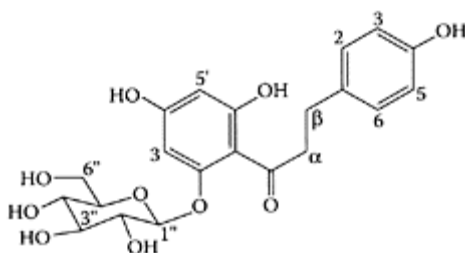
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Apple juice

see also Phloridzin Pearson and coworkers (1999) examined the ability of six commercial apple juices to inhibit copper-catalyzed LDL-oxidation. Their results further support the inclusion of apple and apple products in a healthy diet. In addition, some apple phenolics also inhibited glucose transport *via* the Na-dependent glucose transporter (SGLT1). One such phenolic, phloridzin (phloretin 2'-*O*- β -D-glucoside), a flavonoid dihydrochalcone, is used in studies on glucose transport. Phloridzin and related dihydrochalcones are found in apple products, such as cider (Tomas-Barberan et al.,



Phloridzin. (From Lu and Foo, *Food Chem.*, 61:29–33, 1998. With permission.)

1993). Johnston and coworkers (2002) showed that apple-juice consumption modulated glucose uptake by delaying the intestinal absorption of glucose. Cloudy apple juice,

containing higher levels of phloridzin and other phenols, suppressed glucose absorption in the proximal GI tract to a greater degree than clear apple juice. These researchers suggested that such plant phenols could play a role in determining the glycemic index of plant foods for the treatment of noninsulin-dependent diabetes mellitus (NIDDM). In a recent paper by Andlauer et al. (2004), phloridzin amplified the absorption of the isoflavone genistin in isolated rat small intestine. Because of the cancer-protective effects associated with genistin, a functional food combining soy and apple may provide distinct health benefits.

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Apricot

Apricots were shown to be rich sources of vitamins A and C, β -carotene, and selenium that met the RDAs of healthy individuals (Munzuroglu et al., 2003). In contrast, however, apricots were poor sources of vitamin E. Previous research also showed fresh apricots were significantly higher in selenium compared to other fruits and vegetables by a factor of up to fivefold (Kadrabova et al., 1997; Hussein and Bruggeman, 1999). The anticarcinogenic and antioxidant properties of vitamins A, C, β -carotene, and selenium makes apricots a potentially important functional food and source of nutraceuticals.

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Arabinoxylan

Arabinoxylan, a major component of dietary fiber of cereals, is a hemicellulose composed of a xylose backbone and arabinose side chains (Amodo and Neukom, 1985). The outer layer of wheat bran and the inner layer of the endosperm are both rich sources of arabinoxylans. Lu and coworkers (2000) showed ingestion of arabinoxylan-rich fiber improved postprandial glucose and insulin responses in healthy patients. As a by-product of wheat processing, arabinoxylan-rich fiber could be beneficial for individuals with diabetes or impaired glucose tolerance.

Unlike *Lactobacilli*, *Enterococci*, *Escherichia coli*, *Clostridium perfringens*, or *Clostridium difficile*, which are unable to ferment arabinoxylan, the probiotic *Bifidobacterium longum* strains grew well on it (Crittenden et al., 2002). As a consequence, arabinoxylan has potential to complement *Bifidobacterium longum* strains in synbiotic combinations.

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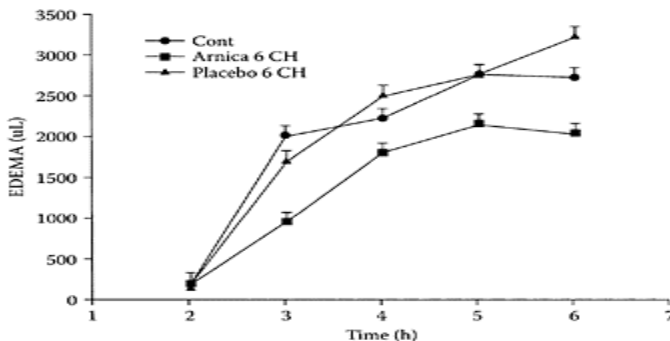


FIGURE A.8 Effect of oral treatment (0.1 mL) with *Arnica montana* 6CH and placebo, administered during three days (three times a day) prior to

injection of carrageenan (1000 µg/paw). * $p < 0.05$. (Macedo et al., *Homeopathy*, 93:84–87, 2004. With permission.)

Arnica

The flowering heads of the Arnica plant have been used in homeopathic medicine for many years. It is a perennial plant that is particularly popular in Germany. Puhlmann et al. (1991) isolated and characterized two homogeneous, immunologically active polysaccharides from *Arnica montana* cell cultures. One was a neutral fucogalactoxyloglucan, while the other was an acidic arabino-3,6-galactan-protein. Fucogalactoxyloglucan exhibited a marked enhancement of phagocytosis *in vivo*, while the acidic polymer showed a strong anticomplementary effect, stimulating macrophages to secrete the tumor necrosis factor (TNF- α). A more recent study by Koo et al. (2000) showed *Arnica montana* had only slight antibacterial activity against 15 oral pathogens *in vitro* compared to propolis. Using the acute carrageenan-induced rat-paw oedema-inflammation model, Macedo et al. (2004) observed a 30 percent inhibition when pretreated with *Arnica montana* 6cH (Figure A.8). Pretreatment of the chronic inflammation model with *Arnica montana* 6cH three days prior to application of nyastatin also significantly ($p < 0.05$) reduced inflammation. The mechanism of action appeared to involve blocking the action of histamine from increasing vascular permeability.

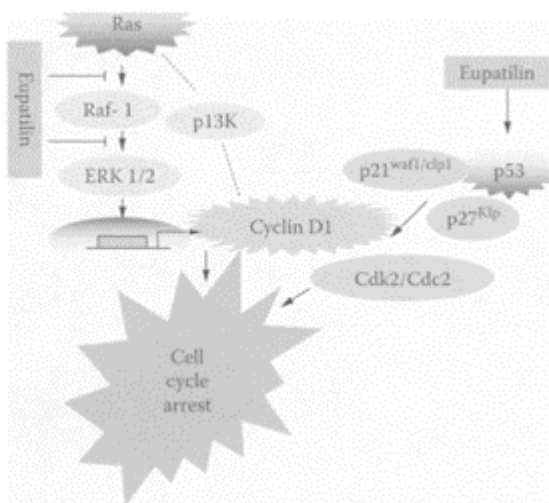
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Artemisia

Many spices belonging to the genus *Artemisia* are also known as aromatic plants. These spices, found in the Middle East, have been used in tonics, stomach, and as tinctures for the relief of rheumatic pains (Paris and Moise, 1971). A sesquiterpene lactone peroxide

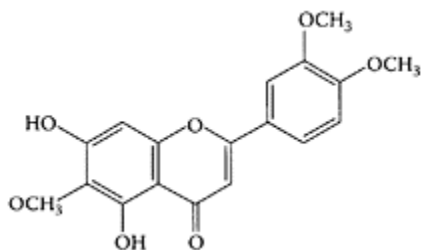
with antimalarial activity was isolated from selected chemotypes in the soil. One of these genera, *Artemisia judaica* L., has long been used in Egypt for medicinal purposes. Very strong antioxidant activity in *Artemisia judaica* L. oil was demonstrated by El-Massry and coworkers (2002), which was attributed to the



SCHEME A.7 Putative mechanism of eupatilin-induced cell-cycle arrest in MCF-10A-*ras* cells. Eupatilin is proposed to inhibit expression of cyclin D1 via the Ras/Raf/MAPK signaling pathway, independently of the Akt pathway. In addition, eupatilin-induced cell-cycle arrest appears to be associated with upregulation of p53 and P^{27kip1}. (From Kim et al., *Biochem. Pharmacol.*, 68:1081–1087, 2004. With permission.)

presence of 2,6-dimethyl phenol (1.39 percent) and camphor (0.38 percent).

Seo et al. (2001) identified eupatilin, a pharmacologically active flavone in extracts from *Artemisia asiatica* Nakai. This flavone was



Eupatilin (5,7-dihydroxy-3',4',6'-trimethoxy flavone). (From Kim et al., *Biochem. Pharmacol.*, 68:1081–1087, 2004. With permission.)

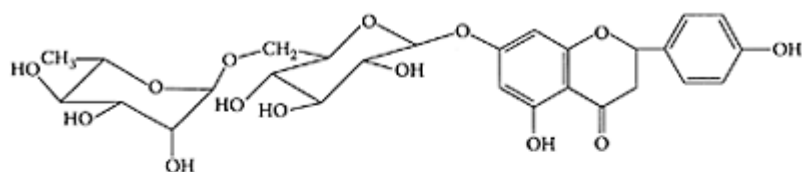
found to induce apoptosis in human promyelocytic leukemia cells. Further studies by Kim and coworkers (2004) showed eupatilin inhibited the growth of H-*ras*-transformed human breast epithelial (MCF10A-*ras*) by modulating key cell-cycle growth regulators. The following scheme suggests eupatilin induces cycle arrest with down-regulation of cyclin D1 (Scheme A.7).

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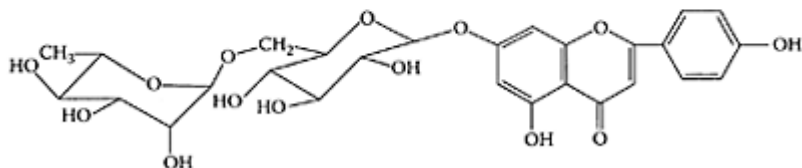
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Artichoke

Artichoke (*Cynara scolymus* L.) is an herbaceous perennial in which the head, an immature flower, is enjoyed as a vegetable throughout the world. Its leaves have been used as an herbal medicine for centuries. An artichoke dry extract was shown by English et al. (2000) to substantially reduce total cholesterol



(Compound 1) (R&S)-narirutin



(Compound 2) apigenin-7-rutinoside

Apigenin-7-rutinoside and narirutin. (Adapted from Wang et al., *J. Agric. Food Chem.*, 51:601–608, 2003.)

and LDL-cholesterol levels in patients with hyperlipoproteinemia by 18.3 percent and 22.9 percent compared to 8.5 percent and 6.3 percent for the placebo, respectively. Perez-Garcia and coworkers (2000) found an artichoke-leaf extract reduced oxidative stress from reactiveoxygen species in human leukocytes. The antioxidant activity was concentration dependent and attributed to the presence of cynarin, caffeic acid, chlorogenic acid, and luteolin in the extract. Pittler and coworkers (2002) showed an artichoke-leaf extract significantly reduced blood cholesterol in patients suffering from hypercholesterolemia compared to the placebo. A growing body of evidence suggests that artichoke-leaf extract is beneficial for the treatment of irritable-bowel syndrome (IBS) and is supported from a surveillance study by Walker and coworkers (2001). The hepatoprotective effects of a water-soluble extract from artichoke (*Cynara scolymus* L.) leaves were shown by Gibhardt (2002) to prevent tauroolithocholate-induced bile canalicular membrane transformations in cultured rat hepatocytes.

The previous studies all focused on artichoke leaves, a known rich source of polyphenols, while the components in the edible portion of the head remained unknown. A recent study by Wang et al. (2003), however, examined the leaves and heads of artichoke for total phenolic compounds, as well as the antioxidative active polyphenols, apigenin-7-rutinoside (compound 1) and narirutin (compound 2). The latter compounds were only found in the heads and increased in more mature vegetables; however, the level of total phenols was overall much higher in the leaves compared to the artichoke heads (Table A.5).

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TABLE A.5

Comparison of Purified Phenolic Compounds and Total Phenolic Content (Percent of Dry Weight) in Artichoke Variety (Green Globe) and Organs, Harvested on Two Dates and Oven- or Freeze-Dried, Based on HPLC Analysis of Methanolic Artichoke Extracts

Organ	1-Caffeoylquinic Acid	Chlorogenic Acid	Luteolin Rutinoideside	Cyaroside	Narirutin	Apigenin 7-rutinoideside	Cyarin	Total
Leaves ^{a,b}	0.149	4.158	0.213	0.314	0	0	1.619	6.455
Leaves ^{a,c}	0.064	4.654	0.275	0.114	0	0	0.924	6.031
Heads								
Young ^{a,b}	0.070	0.459	0.011	0.035	0.085	0.032	0.748	1.44
Young ^{b,d}	0.039	0.276	0.022	0.061	0.108	0.063	0.847	1.416
Mature ^{a,b}	0.020	0.186	0.025	0.024	0.182	0.050	0.309	0.795
Mature ^{b,d}	0.018	0.102	0.04	0.026	0.182	0.076	0.242	0.678

^aHarvested Oct. 3, 2001.

^bOven-dried (70°C).

^cFreeze-dried.

^dHarvested Sept. 5, 2001.

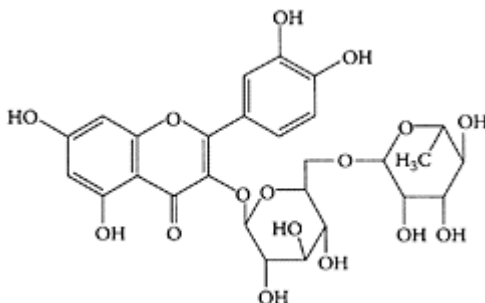
Source: Adapted from Wang et al., *J. Agric. Food Chem.*, 51:601–608, 2003.

Ascorbic acid

see Vitamin C

Asparagus

see also **Rutin** Asparagus (*Asparagus officinalis*) is readily available in grocery stores as canned or freshly packed. The major flavonoid in asparagus is rutin, which is a strong antioxidant (Makris and Rossiter, 2001). Earlier work by Vinson et al. (1998) showed asparagus ranked fourth out of 23 vegetables in the amount of total phenols, but first for antioxidant



Rutin. (Adapted from Deng et al., *Radiat. Phys. Chem.*, 53:629–633, 1998.)

quality. Makris and Rossiter (2001) examined the effect of processing on the flavonol and antioxidant status of asparagus spears. The predominant flavonol was rutin, although a few minor peaks were also observed. The effect of processing is summarized in Table A.6. Boiling was a far more destructive process compared to chopping, with rutin losses being 18.5 percent and 43.9 percent for boiling and chopping, respectively.

Jang and coworkers (2004) recently isolated and characterized a number of natural chemopreventive agents from an ethyl acetate-soluble fraction of the methanol extract of the aerial parts of asparagus (*Asparagus officinalis*). Of 16 compounds identified, two were new natural products, asparagusic acid anti-S-oxide methyl ester and asparagusic acid syn-S-oxide methyl ester plus a new acetylenic compound, 2-hydroxyasaparenyn {3',4'-*trans*-2-hydroxy-1-methoxy-4-[5-(4-methoxyphenoxy)-3-penten-1-ynyl]-benzene}. Of all the compounds identified, linoleic acid showed the most significant activity against COX-2 and moderate activity against COX-1 (Table A.7). Of the remainder, (±)-1-hexadecanoylglycerol (6) exhibited weak activity against COX-1 and moderate activity against COX-2, while ferulic acid (7),

TABLE A.6

Effect of Domestic Processes on Rutin Content of Asparagus¹

Compound	Chopping			Boiling		
	Control	Chopped	Percent Change	Control	Chopped	Percent Change
Rutin	286.5+6.0	233.6+3.5	-18.50 percent	274.1+3.8	153.7+5.5	-43.90 percent

¹Data expressed as mgkg⁻¹

Source: Adapted from Makris and Rossiter, *J. Agric. Food Chem.*, 49:3216–3222, 2001.

TABLE A.7

Inhibitory Activities of Compounds from *A. Officinalis* Against Cyclooxygenase-1 and -2^a

Compound	COX-1		COX-2	
	% inhib at 100 µg/mL	IC ₅₀ (µg/mL)	% inhib at 100 µg/mL	IC ₅₀ (µg/mL)
6	50	ND ^b	67	45.4
7	55	33.7	1	ND
8	62	ND	30	ND
9	51	ND	0	ND
Linoleic acid	100	14.6	100	0.53
trans-resveratrol ^b	100	0.25	100	0.30

^aND Not determined.

^btrans-Resveratrol was used as a positive control.

Source: From Jang et al., *J. Agric. Food Chem.*, 52:2218–2222, 2004. With permission

1,3-*O*-di-*p*-coumaroylglycerol (8) and 1-*O*-feruloyl-3-*O*-*p*-coumaroylglycerol (9) had only weak activity against COX-1. Inhibition of cyclooxygenase (COX) enzymes by nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to hinder the development of colon cancer (Chan, 2002).

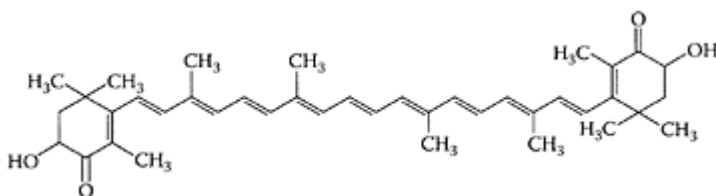
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Astaxanthin

Astaxanthin, a carotenoid pigment, is responsible for the tinted red of crustaceans or the pink flesh of salmon. It is produced commercially worldwide from the microalga *Haemastoccus pluvialis* (Olaizola



Astaxanthin. (From Lai et al., *J. Chromatogr. B.*, 804:25–30, 2004. With permission.)

and Huntley, 2002). The structure of astaxanthin is very similar to β -carotene, but it has been shown to be a superior antioxidant (Lawlor and O'Brien, 1995; Palozza and Krinsky, 1992). Astaxanthin has also been shown to protect the skin and eyes from UV light (Papas, 1999). Other carotenoids, lutein and zeaxanthin, which are also structurally related to astaxanthin, do not have its strong antioxidant activity and UV-light-protective properties (O'Connor and O'Brien, 1998). When fed to humans at doses as low as 3.6 mg per day for two consecutive weeks, astaxanthin protected LDL cholesterol from induced *in vitro* oxidation (Miki et al., 1998). Jacobsson et al. (2004) found that LDL-oxidation time was significantly prolonged in Watanabe heritable hyperlipidemia (WHHL) rabbits in the presence of α -tocopherol but unaffected when treated with astaxanthin. However, the antioxidant treatment produced smaller lesions and intimal thickening. Further examination of atheroma by Li and coworkers (2004) showed astaxanthin had a protective role by reducing macrophage infiltration and modulated macrophage apoptosis and MMP3. A similar effect was evident for α -tocopherol, which suggested these antioxidants are both antiatherogenic, since lipid and macrophage infiltration is closely associated with early plaque development.

Astaxanthin has also been reported to significantly inhibit colon cancer in rats, as well as the enzyme 5- α -reductase involved in prostate growth (Anderson, 2001). The ability of

astaxanthin to cross the blood-brain barrier in rats suggests it might be beneficial to neurological diseases, such as Alzheimer's (Tso and Lam, 1996). Evidence is also accruing regarding the immunomodulating activity of astaxanthin, including enhancement of immunoglobulin production in human blood cells in response to T-dependent stimuli (Jyonouchi et al., 1995). The bioavailability of astaxanthin was demonstrated in humans using a single, high dose of 100 mg and its transport by plasma lipoproteins (Osterlie et al., 2000).

The lipophilic nature of carotenoids, such as astaxanthin, renders it difficult to deliver it to target cells. One way to surmount this problem is to form water-soluble derivatives, such as the disodium salt disuccinate. Hix et al. (2004) showed this astaxanthin derivative was biologically active by upregulating expression of connexin protein (CX43), increasing the formation of CX43 immunoreactive plaques, as well as significantly upregulating intracellular communication. The enhanced delivery of these derivatives suggested greater potential for astaxanthin as an anticancer agent.

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Astragalus

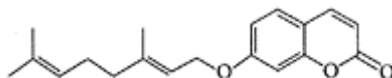
Astragalus, a traditional Chinese herb derived from the root of *Astragalus membranaceus*, has been used to treat diabetes, heart disease, and high blood pressure. An extract from *Astragalus membranaceus* was shown by Zhao et al. (1990) to enhance the immune response in mice. Using a large-scale culture technique, Zheng and coworkers (1998) analyzed the hairy roots of *Astragalus membranaceus*, which contained 5.8 percent and 0.14 percent of crude saponins and astragaloside, respectively. They also demonstrated the ability of the hairy roots to increase immune function. Ma et al. (1998) demonstrated the therapeutic effects of *Astragalus membranaceus* on sodium and water retention in aortacaval fistula-induced heart failure. A clinical research trial by Zheng et al. (1995) showed astragalus improved the deformability of red blood cells and delayed aging in mice.

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Auraptene

Auraptene (7-geranylcoumarin) is a natural component of citrus peel with chemoprotective properties against skin, tongue, esophagus, and colon carcinogenesis in rodents (Murakami et al., 1997; Tanaka et al., 1997, 1998a, b).



Auraptene. (From Tanaka et al., *Carcinogenesis*, 18:2155–2161, 1997.)

Tanaka et al. (1997) reported auraptene reduced the number of precancerous lesions in carcinogen-induced rat colons. A single oral dose of auraptene (200 mg/kg body weight) increased the activity of quinone reductase and glutathione S-transferase, two key Phase II detoxifying enzymes. *In vivo* studies showed auraptene suppressed the generation of superoxide anions (O_2^-) from inflammatory leukocytes. Murakami et al. (2004) found the inhibitory effects of auraptene were due to its selective blockage of the activation stage by attenuating the lipopolysaccharide-induced expression of inducible forms of both nitric oxide synthase and cyclooxygenase in a murine macrophage line, RAW 264.7. It decreased the production of the nitrite anion and prostaglandin E_2 , while suppressing the release of the tumor necrosis factor- α . The overall effect *in vivo* in ICR female rats was decreased levels of edema, H_2O_2 production, leukocyte infiltration, and PCNA-labeling index. *In vivo* data showed a marked suppression of iNOS/COX-2 expression and TNF- α release. Thus, auraptene could have application in preventing and medicating inflammation-related disorders, such as cancer.

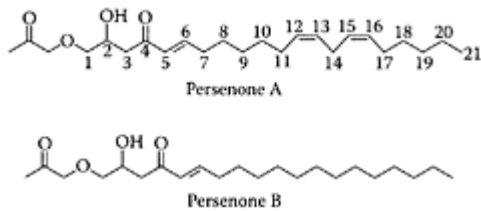
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Avocado

Avocado is a type of pear (*Persea americana*) originating in Mexico that is processed for oil. Mexico (34 percent) is the largest producer of avocados, followed by the United States (8 percent), Israel (4 percent), South Africa (2 percent), and, recently, New Zealand (Eyres et al., 2001). Novel nitric-oxide and superoxide generation inhibitors, persenone A and B, were identified in avocado fruit by Kim and coworkers (2000a). These researchers showed persenone A suppressed expression of



Persenone (From Kim et al., *J. Agric. Food Chem.*, 48:1557–1563, 2000b. With permission.)

both inducible nitric-oxide synthase and COX-2 in mouse macrophages and inhibited H₂O₂ generation in mouse skin (Kim et al., 2000b). Their results suggest that persenone A may prevent inflammation-associated diseases, including cancer. Kawagishi and coworkers (2000) isolated five fatty-acid derivatives in avocado that showed extraordinary, potent liver-injury-suppressing activity against liver damage by D-galactosamine, a powerful liver toxin. The oil from avocado is highly valued by the cosmetic industry and in the food industry for the

TABLE A.8

β-Sitosterol of Eight of the Most Frequently Consumed Fruits in the U.S.A.

Fruit ¹	β-Sitosterol ² (mg/100 g ²)	
Apples		11
Avocado		76
Banana		11

Cantaloupe	8
Grapefruit	13
Strawberries	10
Sweet Cherries	12

¹Raw, edible portion.

² β -Sitosterol values for all fruits, except avocado, Adapted from Moghadasian et al., 1999.

Source: Adapted from Duester, *Lipid Tec.*, 7:84–88, 2001.

beneficial effects of its monounsaturated fatty acid, oleic acid, which accounts for almost 80 percent of the total fatty acids. In addition, avocado oil also contains relatively high amounts of β -sitosterol (0.5–1.0 percent) reported to lower blood cholesterol levels (see Phytosterols). β -Sitosterol has also been attributed to alleviating the symptoms of benign prostatic hypertrophy in men over 50 years of age (Berges et al., 1995). Avocado appears to be one the richest sources of β -sitosterol compared to eight of the most popular fruits consumed in the United States, as seen in Table A.8. Lu and coworkers (2005) showed lipid-soluble bioactives in avocado extract inhibited the growth of prostate-cancer cells.

Avocado was also shown to have important antihyperglycemic properties in humans (Alvizouri-Munoz et al., 1994). Using an *in vitro* method for assessing glucose diffusion across the gastrointestinal tract, Gallagher and coworkers (2003) showed avocado decreased glucose movement by more than 50 percent. These researchers suggested that avocado could be used as a dietary supplement in the diet of type 2 diabetic subjects.

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B

Baicalein and Baicalin

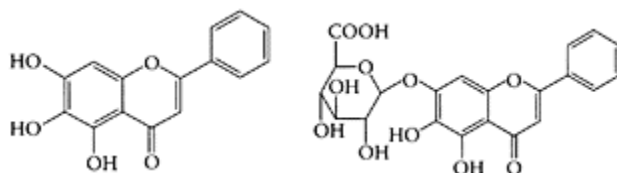
Baicalin, a flavonoid with a structure analogous to genistein, is found in *Scutellaria* species used widely in Chinese herbal medicine. It has a glucuronate group at the C-7 position, which is absent in its aglycone, baicalein. Baicalein and baicalin both appear to have antiviral (Kitamura et al. 1998), antioxidant (Shi et al., 1995), antitumor (Matsuzaki et al., 1996), and anti-inflammatory (Lin and Shieh, 1996) properties, as well as an ability to reduce blood pressure and relax arterial smooth-muscle cells (Chen et al., 1999). The antitumor effects of baicalin on human hepatoma cell lines was also reported by Motoo and Sabatu (1994). Po and coworkers (2002) showed baicalin, unlike genistein, suppressed 17 β -estradiol-induced transactivation in MFC-7 cells expressing receptor a. Baicalin also proved to be a stronger apoptosis-inducing agent, making it a superior chemopreventive agent. Chan and coworkers (2000) reported baicalin induced apoptosis in several human prostate-cancer cell lines so that it had the potential to be a chemopreventive agent or an adjuvant for the treatment of prostate cancers.

Baicalin and baicalein were both found by Huang and coworkers (2004) to exhibit novel vascular effects by inhibiting endothelial aortic relaxation *via* inhibition of cyclic GMP accumulation in vascular smooth-muscle cells. If this occurred in small blood vessels, vascular permeability would be reduced, which may explain the anti-inflammatory action of these flavonoids against acute edema or by inhibiting lipoxigenase, a key enzyme involved in inflammatory response.

Shen and coworkers (2003) evaluated the mechanisms responsible for the anti-inflammatory properties of baicalin and baicalein in human leukocytes. They both reduced *N*-formyl-methionyl-leucyl-phenylalanine (fMLP)-and phorbol-12-myristate-13-acetate (PMA)-induced reactive-oxygen intermediates in neutrophils and monocytes. The anti-inflammatory activity of baicalin and baicalein was due to the combination of baicalin scavenging the reactive-oxygen intermediates and baicalein antagonizing ligand-initiated Ca²⁺ influx, both of which inhibit Mac 1-dependent leukocytes.

Li et al. (2000) reported that baicalin inhibited HIV-1 infection by interfering with the interaction of HIV-1 envelope proteins with chemokine coreceptors, blocking the entry of HIV into target cells. As a result, it is viewed as a possible natural chemotherapy for HIV infection (De Clerq et al., 2000). Recent studies by Wang and coworkers (2004) showed that coupling baicalein (BA) with zinc made it a far more effective inhibitor of recombinant reverse transcriptase (RT) and HIV-1 entry into the host cells. Figure B.9 shows that inhibition of recombinant RT was far greater in the presence of lower

concentrations of BA-Zn with an EC₅₀ 25.09 μ M which was threefold lower than the EC₅₀ for BA of 83.48 μ M.



Baicalein and Baicalin. (From Zhang et al., *J. Pharmaceut. Biomed. Anal.*, 36:637–641, 2004. With permission.)

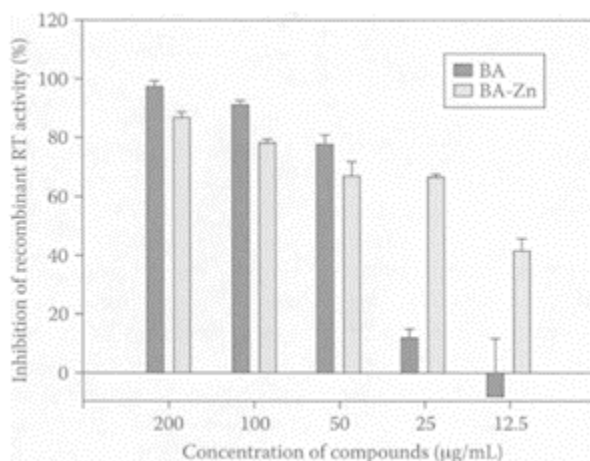


FIGURE B.9 Inhibition of recombinant HIV-1 RT activity by BA and BA-Zn. Inhibition rates were calculated according to the absorbance of the ELIZA Reader. Data expressed as means \pm SEM of at least three independent measurements. (From Wang et al., *Biochem. Biophys. Res. Commun.*, 324:605–610, 2004. With permission.)

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TABLE B.9

Effect of Various Fruit Extracts or Juices on NO Synthesis in Human Red-Cell Membrane

Addition to the Assay Mixture	nmol NO Produced/h/mg Residue
None	0.012±0.005
Banana	8.45±1.15
Cucumber	6.36±0.057
Apple	6.07±1.14
Lemon	6.05±1.15
Pear	3.42±0.14
Orange	2.57±1.58

Grape (purple)	2.1±0.054
Grape (green)	0.1±0.011

Note: Results are the mean±S.D. of six different experiments, each conducted in triplicate.

From Guha et al., *Nutr. Res.*, 23:1081–1088, 2003. With permission.

Banana

Bananas (*Musa Cavendish*), one of the most popular fruits worldwide, is a source of antioxidants, vitamin C, vitamin E, and β -carotene. Someya and coworkers (2002) found bananas were also high in flavonoids, with the peel being a richer source of total phenolics (907 mg/100 dry wt) compared to the pulp (232 mg/100g dry wt). This difference was reflected by the antioxidant activity of the peel extract being 2.2 times greater than the pulp. Several flavonoids were identified, including gallocatechin, catechin, and epicatechin. Of these, gallocatechin exhibited the greatest antioxidant activity and was much higher in banana peel (158 mg/100 g dry weight) compared to the pulp (29.6 mg/100 g dry weight). These researchers recommended that banana peels be considered a functional food source for combating chronic diseases and should not be discarded.

A study in India by Guha et al. (2003) showed ripe banana (*Musa paradisiacal sapientum*) extracts stimulated the production of nitric oxide (NO) in human erythrocyte membranes. Nitric oxide is tumoricidal, as well as induces apoptosis and differentiation in neoplastic cells (Farias-Eisner et al., 1994; Jun et al., 1996). Stimulation of nitric oxide is catalyzed by a family of isoenzymes, nitric synthase (NOS). Incubation of human red-cell membranes with different fruit extracts showed ripe banana was the most potent stimulator of NO, followed by cucumber, apple, and lemon, with pear lacking any activity (Table B.9). Inclusion of ripe bananas in the diets of mice administered Ehrlich's ascetic carcinoma cells showed that 70 percent of those animals receiving 2 g of ripe banana (wet weight/day) died within 35 days compared to the control group which died within 5–6 days. The ability of bananas to prevent or slow down the progression of ascetic carcinoma in mice could be extended to humans.

Vitamin A deficiency and chronic diseases are a particularly serious problem in Pacific Island countries. A recent paper by Englberger and coworkers (2003) pointed out the importance of bananas as significant sources of provitamin A and β - and α -carotenes, which could alleviate this problem in Micronesia.

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Barley

Barley is one of the major cereals grown worldwide and is particularly important in China. The major uses for barley are in malting, as well as for the feed industry. Germinated barley foodstuff (GMF) obtained from the aleurone layer and scutellum fractions of malt consists mainly of dietary fiber and glutamine-rich protein. This material was found to have a preventive and therapeutic effect in an experimental colitis model (Kanauchi et al., 1997, 1998), as well as in patients with mild to moderate ulcerative colitis (Mitsuyama et al., 1998). Bamba and coworkers (2002) fed germinated barley to patients with mild to moderate active ulcerative colitis and found significant clinical and endoscopic improvements were associated with an increase in stool butyrate levels. These results suggested GMF was a new prebiotic for the treatment of ulcerative colitis. Deguchi and coworkers (2000) produced an anthocyanintannin type pigment from barley bran-fermented broth. The purple pigment, referred to as hordeumin, scavenged superoxide radicals in a dose-dependent manner, which was attributed to the bran poly phenols, such as proanthocyanidins.

Barley is also a good source of β -glucan, the mixed-linked (1 \rightarrow 3), (1 \rightarrow 4)- β -D-glucan, which has been shown to have important health benefits. The β -glucan content of winter-barley cultivars grown in different locations in China were similar to those grown in Canada and Australia (Zhang et al., 2002). Because of the significant interaction between cultivars and environment on β -glucan content, they emphasized the importance of planting appropriate barley cultivars in specific areas in order to maximize β -glucan levels.

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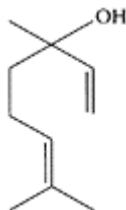
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Basil (*Ocimum basilicum*)

Basil (*Ocimum basilicum* L.Lamiaceae) is a common herb used for culinary and medical purposes. The essential oil obtained from basil was reported to exhibit antimicrobial activity, as well as inhibit the fungus *Aspergillus ochraceus* and the production of ochratoxin A (Hili et al., 1997; Basilico and Basilico, 1999). A recent study by Opalchenova and Obreshkova (2003) identified the main components in basil by gas chromatography as linalool (59.5 percent), methylchavicol (12 percent), and methylcinnamate (7.2 percent). They also examined whether basil could inhibit multidrug-resistant clinical isolates of the genera *Staphylococcus*, *Enterococcus*, and *Pseudomonas*. Basil proved



Linalool. (From Letizia et al., *Food Chem. Toxicol.*, 41:943–964, 2003.
With permission.)

effective against these antibiotic-resistant tested bacteria with minimum inhibitory concentrations ranging from 0.0030–0.0007 percent.

Basil oil was also reported to exhibit antiinflammatory properties against carrageenan, PGE₂, leukotriene, and arachidonic acid-induced paw edema in rats (Singh, 1998, 1999 a, b, c). Courreges and Benecia (2002) further explored possible immunomodulatory effects of basil oil on mouse macrophages. Exposure of macrophages to basil oil for a 24-hour period significantly inhibited phagocytosis, with complete inhibition with dilutions of 1:2000 and 1:1000 (Table B.10).

Javanmardi et al. (2003) screened 23 Iranian basil samples as sources of antioxidants and phenolics. They found them to be good sources of antioxidants because of their strong radical-scavenging activities. A positive linear relationship was observed between antioxidant activity and total phenolic acids for the basil samples examined.

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TABLE B.10

Effect of Basil Oil and Phagocytic Activity and Respiratory Burst in Mouse Peritoneal Macrophages

Basil-oil Dilution	Percent of Phagocytosis	Percent Cells Including Precipitated Formazan
1:1000	0.6±0.6 ¹	0.4±0.6 ¹
1:2000	0.4±1.3 ¹	3.4±1.3 ¹
1:4000	45.2±3.7 ¹	43.6±5.2 ¹
1:8000	78.3±6.6 ²	82.2±4.7 ²
1:16000	89.4±5.1 ^{ns}	92.7±5.3 ^{ns}
Control	96.8±5.8	98.3±7.4

¹*p*<0.005; ²*p*<0.05; ^{ns}Not significant.

Source: From Courreges and Benecia, *Fitoterapia*, 73:369–374, 2002. With permission.

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Beans

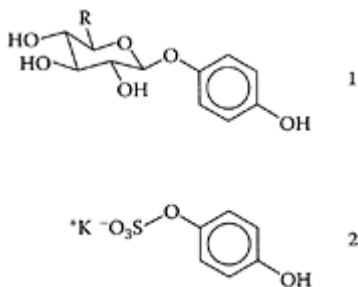
Beans are an important part of our diet and represent a good source of protein and nutrients. The consumption of beans, particularly in Mexico, has a long history and was estimated at 19.5 kg/annum per capita (Gonzalez de Mejia, 1990). The importance of phenolic compounds in plant foods, including beans, is related to their effect on nutritional and esthetic properties. In addition to their antioxidant and chelating properties, they are able to scavenge reactive-oxygen species and electrophiles, as well as modulate cellular-enzyme activities (Huang and Ferraro, 1992). The antimutagenic properties of the phenolic compounds from common beans (*Phaseolus vulgaris*) were reported by Gonzalez de Maija et al. (1999). The majority of poly phenols were located in the seed coat with negligible amounts in the cotyledons. The key antimutagenic compounds in beans, easily extracted with methanol, were phenols, while low-molecular-weight hydrolyzable phenols were present in the aqueous extract. The phenolic compounds specifically identified were catechin, tannic acid, and ellagic acid. These compounds were effective against the mutagenic activities of 1-nitropyrene (1-NP) and benzo[α]pyrene using the *Salmonella typhimurium* tester strain YG1024 in the plateincorporation test. Dose-dependent inhibition was observed for all the samples tested. Doses of 500 μ g equivalent catechin/plate resulted in 63%, 81%, and 83% inhibition for water, water/methanol, and methanol extracts, respectively. The greatest inhibition was evident for the methanol extract at lower doses of 50 μ g equivalent catechin/plate. These results were consistent with earlier findings by Mandal and coworkers (1987) regarding the antimutagenic effects of ellagic acid.

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Bearberry

see also Uva-ursi Bearberry (*Arctostaphylos uva-ursi* L.) is a small shrub that grows in the northern latitudes and high mountains of Europe, Asia, and America. Its astringent leaves have medicinal properties and are used as a disinfectant in the treatment of lower urinary-tract infections. One of the principal components of bearberry-leaf extracts is arbutin (hydroquinone-1-*O*- β -D-glucoside), which forms urinary metabolites that are conjugates with glucuronic and sulfuric acids (Paper et al., 1993; Siegers et al., 1997). These metabolites appear to be precursors of hydroquinone, which is released in the lower urinary tract where it kills or inhibits bacteria. Pegg and coworkers (2001) reported the presence of a natural antioxidant in the ethanol extracts of bearberry leaves, which proved to be very effective in nitrite-free processed meats. Bacterial surface hydrophobicity appears to be related to the ability of certain pathogens to cause infection. Thus, an increase in hydrophobicity is strongly correlated with enhanced pathogenic potential (Absolom, 1988; Andersson et al., 1998). Altering surface hydrophobicity could provide an effective way of decreasing the viability of pathogenic bacteria in food or in the



Arbutin (1, $\text{R}=\text{CH}_2\text{OH}$) and hydroquinone glucuronide (1, $\text{R}=\text{COOH}$) and hydroquinone sulfate potassium salt (2). (From Glockle et al., *J. Chromatogr. B*, 761:261–266, 2001. With permission.)

gastrointestinal tract. Annuk et al. (1999) compared aqueous extracts of four medicinal plants, including bearberry, on the cell surface hydrophobicity of the Gram-negative pathogen *Hylobacter pylori*. Bearberry extract proved to be the richest source of tannic acid and was attributed for the decrease in cell surface hydrophobicity and its antibacterial activity against *Hylobacter pylori*. Recent work by Dykes and coworkers (2003 a) examined the effect of an antioxidant ethanolic extract from bearberry leaves on the surface hydrophobicity of 25 food-related bacteria. The bearberry extract significantly decreased the hydrophobicity of only four bacteria, while significantly increasing the hydrophobicity of 14. These researchers cautioned against marketing a particular extract, such as bearberry, based on a single claim, as there may be detrimental effects on food-related bacteria associated with such nutraceuticals. For example, increased antibiotic resistance in bacteria was recently associated with their exposure to certain nutraceutical

extracts (Ward et al., 2002). However, Dykes et al. (2003b) also studied the effect of an ethanolic extract from bearberry, alone or in combination with nisin, on 25 food-related bacteria. Although bearberry did not exhibit any antimicrobial activity, it enhanced the antibacterial efficacy of nisin against Gram-positive bacteria, particularly *Brochothrix thermosphacta*.

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Beer

Epidemiological studies showed an inverse relationship between moderate ethanol consumption and risk of coronary heart disease

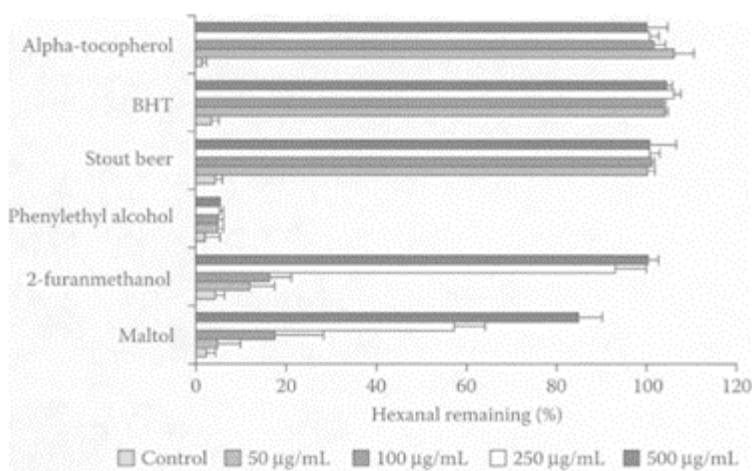


FIGURE B.10 Relative amounts of hexanal remaining in hexane samples containing volatiles, (a) phenylethyl alcohol; (b) 2-furanmethanol; (c) maltol. (From Wei et al., *J. Agric. Food Chem.*, 49:4097–4101, 2001. With permission.)

(Gronback et al. 1995; Kannel and Ellison, 1996). Reduced mortality was associated with the consumption of beer and wine but not with spirits. An increase in plasma antioxidant levels was reported by Ghiselli and coworkers (1999) in healthy, fasting nonsmokers consuming 500 mL beer in the morning. The antioxidants present in beer were phenolic acids, of which syringic and sinapic acids were the most significant. Wei et al. (2001) examined the antioxidant properties of volatiles extracted from stout beer, particularly phenylethyl alcohol, maltol, and 2-furanmethanol. Measuring antioxidant activity, as the reduction in the oxidation of hexanal to hexanoic acid, 2-furanmethanol and maltol were far more effective in preventing hexanal oxidation compared to phenylethyl alcohol (Figure B.10).

In addition to polyphenols, Gorinstein et al. (2002) reported the presence of protein and amino acids in beer. To assess whether these proteins were biologically active, these researchers examined the effect of lyophilized polyphenol-free beer and lyophilized polyphenol-free wine on rat-plasma lipids over four weeks. Only the group fed the diet supplemented with beer significantly lowered total cholesterol, LDL cholesterol, and triacylglycerols, pointing to the potential contribution by the proteins and essential amino acids present in beer. Thus, moderate consumption of beer appears to be as beneficial as moderate consumption of wine.

Arimoto-Koyabashi and coworkers (1999) found native and freeze-dried Japanese-beer samples inhibited the genotoxicity of several heterocyclic amines and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG). Kimura et al. (1999) isolated an antimutagen in beer,

glycine betaine, but it had no effect on MNNG. However, the first nucleoside with antimutagenic properties against MNNG was reported by Yoshikawa et al. (2002) who identified a pseudouridine compound in one of six antimutagenic fractions isolated from freeze-dried beer. Pseudouridine was present at around 0.4 mg/100 mL beer but only accounted for 3 percent of the beer's total antimutagenicity. The major compounds responsible for the bioactive properties of the beer still remained to be identified.

Nozawa et al. (2004) reported the inhibitory effects of four commercial beers, two pilsner-types, a black beer, and a stout beer, against five heterocyclic amine carcinogens. They all exhibited antimutagenic properties by inhibiting the genotoxic effects of these carcinogens, as well as significantly reducing the number of ACF in rats fed a diet containing these carcinogens.

Bamforth (2002), in reviewing the nutritional properties of beer, noted its contribution to certain B vitamins, minerals, antioxidants, and possibly fiber.

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Beets (*Beta vulgaris*)

see also Betalains Red beets are very popular vegetables used for the production of such ethnic foods as borscht. Kapadia and coworkers (1996) showed a root extract from red beet exhibited the strongest *in vitro* inhibitory effect on Epstein-Barr virus early antigen (ENV-EA) induction using Raji cells compared to capsanthin, cranberry, red onion skin, and short and long red bell peppers. The root extract also significantly inhibited tumors in mice skin and lungs. Bobek et al. (2000) fed diets supplemented with 15 percent fiber isolated from red beet to Wistar rats with hypercholesterolemia and chemically induced colon cancer. The red-beet diet significantly reduced serum cholesterol (-30 percent) and triacylglycerol (-40 percent) levels while significantly increasing HDL cholesterol. In addition, the number of animals bearing tumors was reduced by 30 percent, although it did not significantly affect the incidence of colon tumors.

Kanner and coworkers (2001) identified a new class of dietary cationized antioxidants in red beets, the betalains. The major one was betanin, a betanidin 5-*O*- β -glucoside. A relatively low concentration of betanin was found to inhibit lipid peroxidation of membranes or linoleate emulsion by the “free iron” redox cycle, H₂O₂-activated metmyoglobin, lipoxigenase. The bioavailability of betanin was demonstrated by the presence of betacyanin in the urine of four volunteers 2–4 h following the consumption of 300 mL of red beet juice containing 120 mg of the antioxidant.

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Bell pepper (*Capsicum annuum*)

see also Chili Peppers and Peppers Bell pepper is used extensively in North Africa as a spice to enhance the flavor of food. Its juice was shown to inhibit *N*-methylnitrosourea-induced colon carcinogenesis in rats (Narisawa et al., 2000). Maoka and coworkers (2001) found that the

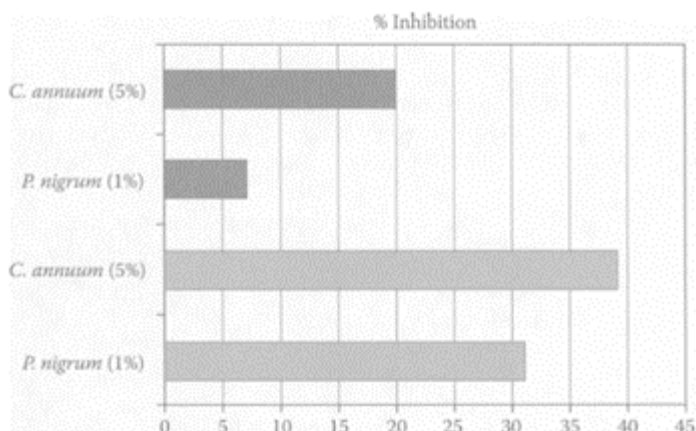


FIGURE B.11 Pre-treatment effect with bell (*C.capsicum*) and black (*P.nigrum*) peppers on the mutagenicity of 10 mM EC (shaded) and 0.005 percent MMS (black). (Adapted from El Hamss et al., *Food Chem. Toxicol.*, 41:41–47, 2003. With permission.)

carotenoids obtained from the fruits of bell peppers exhibited potent antitumor properties both *in vivo* and *in vitro*. Carotenoids from bell pepper were previously shown to inhibit the mutagenicity of 1-nitropyrene, 1,6-dinitropyrene, and 1,8-dinitropyrene by 87 percent, 79 percent, and 73 percent, respectively (Gonzalez de Meija et al., 1998). Capsaicin, a major component in bell pepper, was shown to inhibit mutagens and carcinogens by modulating cytochrome P450 monooxygenases (Miller et al., 1993). El-Hamss et al. (2003) recently showed bell pepper had strong chemopreventive properties by its antimutagenic effect against promutagen ethyl carbamate (EC) and against the alkylating agent methyl methanesulfonate (MMS) in larvae of *Drosophila melanogaster*, using the wing Somatic Mutation and Recombination Test (SMART). The 2-day-old larvae were pretreated with bell and black peppers 24 h prior to treatment with EC and MMS. In the presence of 5 percent bell pepper, there was a significant reduction ($p < 0.05$) in mutational events by 39 percent from the original 1.02 spots/wing in the presence of EC (10 mM). This was somewhat greater than the 20 percent reduction of wing/spots in the presence of 5 percent bell pepper from the original 4.60 spots/wing in the presence of 0.005 percent MMS (Figure B.11). Black pepper was only effective in reducing mutations induced by EC. The inhibitory effect was attributed to such compounds as β -carotene, together with small amounts of capsaicin.

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Berries

see also Individual berries Berries are rich sources of phenolic pigments and anthocyanins. They are relatively high in phenolic antioxidants, which correlates with their

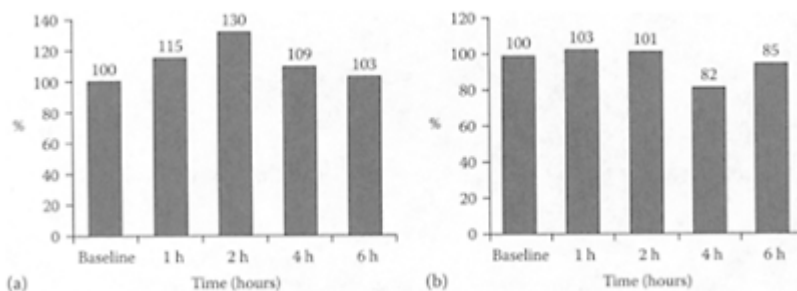
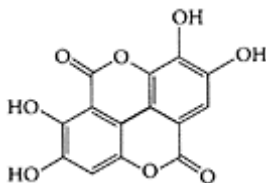


FIGURE B.12 (a) Relative changes in plasma antioxidant after juice consumption, (b) Relative changes in plasma MDA after juice consumption. (From Netzel et al., *Food Res. Intern.*, 35:213–216, 2002. With permission.)

anthocyanin and phenolic compounds (Heinonen et al., 1998; Prior et al., 1998). Berries, such as strawberries and black raspberries, have been shown to have chemopreventive properties against cancers. Ellagic acid, a major component in these fruits, was found to

inhibit carcinogenesis in *in vitro* and *in vivo* studies. Xue et al. (2001) reported that in addition to ellagic acid, a methanolic extract of strawberries and

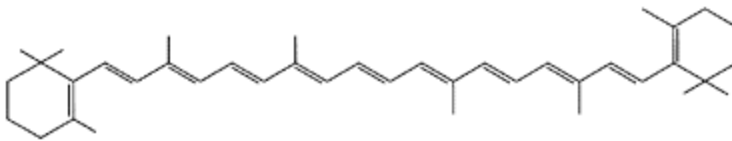


Ellagic acid. (Adapted from Mertens-Talcott and Percival, *Cancer Lett.*, 218:141–151, 2005.)

black raspberries also displayed chemopreventive properties. Miranda-Rottmann and coworkers (2002) showed Chilean berry [*Aristotelia chilensis* (*ach*)] was much higher in phenolics than blackberry, cranberry, and strawberry, with much higher scores for total radical-trapping potential (TRAP) and other *in vitro* antioxidant capacity tests. The anthocyanins present in *ach* juice prevented copper-induced LDL oxidation, indicating its possible antiantherogenic properties. Netzel et al. (2002) demonstrated the ability of a composite antioxidant-rich juice (30 percent grape, 25 percent black currant, 15 percent elderberry, 10 percent sour cherry, 10 percent blackberry, and 10 percent aronia) to significantly increase the plasma antioxidant activity (30 percent after 2 h) and significantly reduce plasma MDA (18 percent after 4 h) in six healthy volunteers (Figure B.12 a, b).

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All trans- β -carotene. (Adapted from Keijer et al, *Biochem. Biophys. Acta*, 1740:139–146, 2005)

β -Carotene

β -Carotene is an important antioxidant present in fruits and vegetables. As a carotenoid it is a potent quencher of singlet oxygen and would be expected to exert a protective effect against sunlight-induced erythema in human skin (Gollnick et al. 1996; Biesalski and Obermiller-Jevic, 2001) and photoimmunosuppression (Fuller et al., 1992; Herraiz et al., 1992). Trekli and coworkers (2003) examined the effect of β -carotene on UVA-induced HO-1 gene expression in a cultured human fibroblast line FEK4. Activation of the HO-1 gene has become a sensitive marker for oxidative stress. These researchers showed β -carotene inhibited activation of the HO-1 gene, probably through scavenging singlet oxygen.

Considerable controversy surrounds β -carotene, as three randomized clinical trials showed that it alone, or in combination with vitamins A and E, increased lung-cancer incidence and mortality in heavy smokers and in asbestos workers (The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994; Stram et al., 2002; Omenn et al., 1996a, b). Paolini et al. (2003) reviewed the data on β -carotene and suggested it was harmful when given as the sole supplement to smokers or individuals exposed to environmental carcinogens. The high levels of cytochrome P450 isoforms induced by β -carotene under these conditions could predispose individuals to higher cancer risk as a result of bioactivation of procarcinogens or by increased production of reactive-oxygen species. Thus, β -carotene may act as a cocarcinogen, particularly in individuals exposed to tobacco smoke or industrial settings. However, under normal circumstances, β -carotene exhibits both antioxidant and anticancer properties.

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Betalains

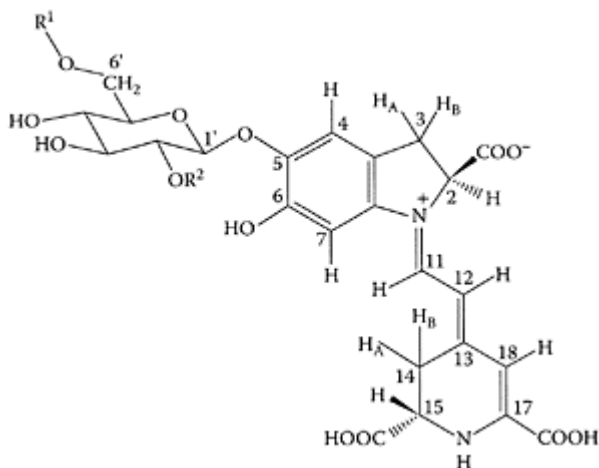
Betalains are water-soluble pigments containing nitrogen and include red-violet betacyanins and yellow betaxanthins. Betacyanins are a group of compounds exhibiting antioxidant and radical-scavenging activities (Escribano et al., 1998; Pedrano and Escribano, 2000). Betalains are a class of cationic antioxidants found in red beets. One of the major ones, betanin or betanidin 5-*O*- β -glucoside, was shown by Kanner and coworkers (2001) to inhibit linoleate peroxidation with an IC_{50} value of 0.4 μ M compared to 1.2 and 5.0 for catechin and α -tocopherol, respectively. Betanin ($IC_{50} < 2.5 \mu$ M) inhibited lipid peroxidation of membranes or linoleate emulsions catalyzed by the “free iron” redox cycle, H_2O_2 -activated metmyoglobin or lipoxygenase and was more effective than catechin. The bioavailability of betanin was demonstrated in four volunteers with 0.5–0.9 percent detected in the urine. An excellent review of betalain was published by Strack and coworkers (2002).

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Bilberry

Bilberry, a low-growing shrub, grows mainly in the U.K., northern Europe, and Asia. Its dark-blue berries are used mainly for tarts and preserves. The main phenolic constituents in bilberry (*Vaccinium myrtillus* L.) are anthocyanins. Madhavi et al. (1998) identified



Betanin ($R^1=R^2=H$). (From Strack et al., *Phytochemistry*, 62:247–269, 2002. With permission.)

TABLE B.11

DPPH Radical-Scavenging Activity, Total Phenolic, and Anthocyanin Contents in Berry Extracts

Total Phenolics (mg/g)	Anthocyanin (mg/g)	DPPH Radical-Scavenging Activity (μmol of Trolox/g)
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Bilberry	55.1±1.0	26.3±1.5	287.9±10.3
Blackberry	42.5±0.3	10.0±0.6	238.5±5.9
Black Currant	40.9±0.7	15.3±0.7	200.3±3.3
Raspberry	39.0±0.6	4.4±0.2	208.0±8.5
Lowbush Blueberry	35.9±0.4	12.1±0.5	178.1±5.4
Cowberry	35.4±0.1	6.1±0.4	196.9±6.4
Highbush Blueberry	26.4±0.4	6.3±0.4	128.4±8.2
Strawberry	22.5±0.2	2.4±0.2	121.6±4.5
Cranberry	20.1±0.4	3.1±0.2	92.9± 2.3
Red Currant	13.0±0.1	2.3±0.1	71.3±3.4

Source: From Katsube et al., *J. Agric. Food Chem.*, 51:68–75, 2003. With permission.

a major flavonoid fraction containing proanthocyanidins and anthocyanin pigments together with a hexane extract containing chlorophylls, carotenoids, sterols, and lipids in tissues extracted from bilberry fruits and callus cultures. Many of these constituents not only protected against initiation of carcinogenesis but prevented proliferation of the cancer cell lines. This was evident by the ability of the hexane extract to induce the phase II xenobiotic detoxification enzyme, quinone reductase (QR), in murine hepatoma cells.

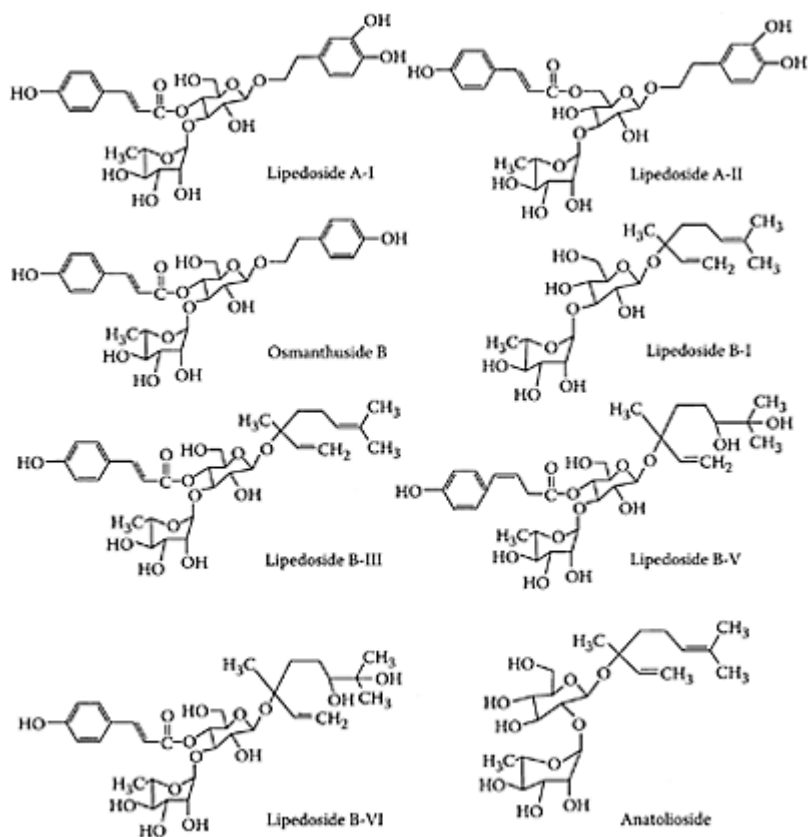
A study by Logan and Wong (2001) showed bilberry may be beneficial in the treatment of chronic-fatigue syndrome through its control of oxidative stress. Head (2001) suggested a number of botanicals, including bilberries, could also prevent cataracts, particularly by inhibition of aldolase reductase activity. Katsube et al. (2003) recently reported that the phenolic and anthocyanin content, as well as DPPH radical-scavenging activity, was highest in the bilberry extract (Table B.11). Those anthocyanins eluted with 20–40 percent and 40 percent metanol were the more potent inhibitors of the growth of human promyelocytic leukemia HL60 and HCT116 cancer cells, inducing apoptosis in the HL60 cells. The anticancer effects exhibited by bilberries make them a potential functional food.

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Bitter tea (*Ligustrum pedunculare*)

Bitter tea is a popular beverage in China. In contrast to green and oolong teas, which are prepared from the leaves of *Camellia sinensis*, bitter tea is brewed from the leaves of 10 species in five different families (He et al., 1992). Wong and coworkers (2001) characterized the antioxidants present in one of these species, *Ligustrum purpuracens*, as two phenylethanoid glycosides, acteoside and ligpurposide A. Both



SCHEME B.8 Structures of phenylethanoid and monoterpenoid glycosides in bitter-tea beverage derived from the plant *L. pedunculare*. (From Chen et al., *J. Agric. Food Chem.*, 50:7530–7535, 2002. With permission.)

proved to be effective antioxidants comparable to green tea catechins. Further work by Chen and coworkers (2002) characterized the antioxidants in *Ligustrum pedunculare*, another species used for brewing bitter tea in Suchuan Province of China. He et al. (1994) previously isolated eight phenylethanoid or monoterpene glycosides in this species. Chen and coworkers (2002) showed the crude glycoside fraction prevented the oxidation of human low-density lipoprotein (Scheme B.8). Four out of the eight monoterpene glycosides (lipedosides B-V, B-VI, A-I and A-II) protected LDL from Cu²⁺-mediated oxidation, as well as exhibited free-radical scavenging activity on DPPH equivalent to that of α -tocopherol (Figure B.13).

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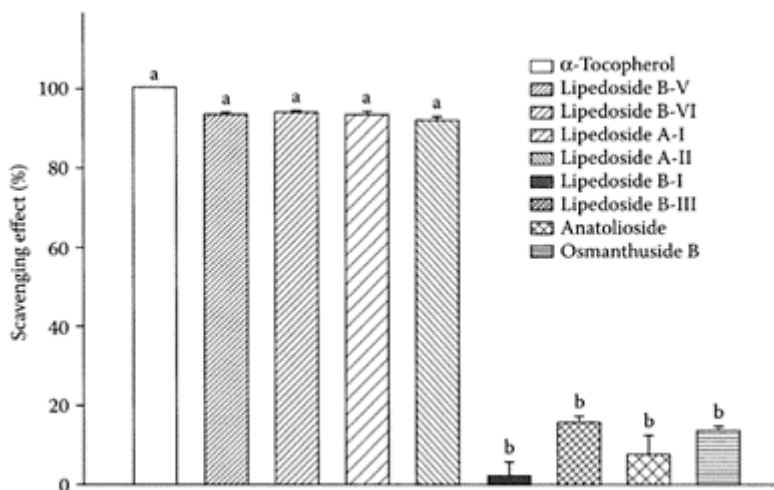


FIGURE B.13 Free-radical-scavenging effects of eight phenylethanoid or monoterpene glycosides (10 μ M) isolated from *L. pedunculare*. 2,2-Diphenyl-1-picrylhydrazyl DPPH was used as a stable free radical, α -Tocopherol was

used as a reference antioxidant. Means with different letters (a, b) differ significantly at $p < 0.05$. (From Chen et al., *J. Agric. Food Chem.*, 50:7530–7535, 2002. With permission.)

Black beans

Carmona et al. (1996) showed that condensed tannins isolated from black beans strongly inhibited α -amylase, maltase, sucrase, and lactase enzyme activities *in vitro*. The tannins also affected *in vitro* glucose uptake by rat-everted intestinal sleeves, which could explain the reduction in carbohydrate bioavailability found in animals fed high tannin diets. Chao and coworkers (1998) showed that water and organic-solvent extracts of black bean exhibited much higher antioxidant capacity compared to equivalent extracts from soybeans. The ability to inhibit LDL oxidation in plasma of patients suffering from cardiovascular disease was positively correlated with GSH, genistein, anthocyanin, and TAS in the water extract, and vitamin E, genistein, and anthocyanin in the organic extracts for all treatments.

The ability of black beans to bind bile acids *in vitro* was examined by Kahlon and Woodruff (2002). The cholesterol-lowering properties of food components can be predicted from their ability to bind bile acids, which in turn lowers the risk of cardiovascular disease. These researchers found that both black beans and pinto beans had much higher bile-acid-binding properties compared to soybean protein, suggesting black beans have important health-promoting properties. Recent research by Bawadi et al. (2004) showed that the water-soluble condensed tannins isolated from black beans inhibited the growth of Caco-2 colon, MCF-7 and Hs578T breast, and DV145 prostatic cancer cells without affecting normal human fibroblast lung cells.

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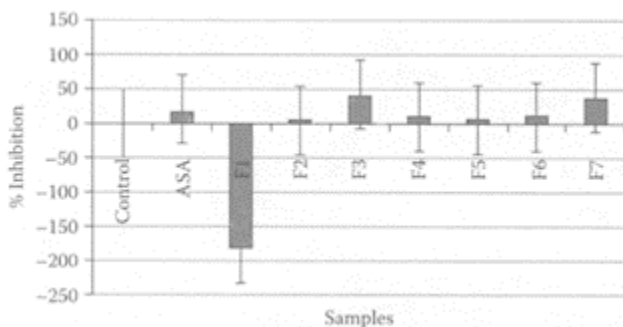


FIGURE B.14 Histogram of inhibition of hyaluronidase by crude extract (F1) and fractions (F2-F7) from chromatographic separation of blackberry fruit. (From Marquina et al., *Fitoterapia*, 73:727–729, 2002. With permission.)

Blackberry (*Rubus fruticosus* B.)

Blackberry is a small tree with red-blackish berries rich in polyphenols (Otaiza, 1997). It was reported that blackberry fruit exhibited antiinflammatory activity (Thinquino, 1993). Marquina et al. (2002) assessed the anti-inflammatory activity of a number of different aqueous extract fractions from blackberry based on their ability to inhibit hyaluronidase activity. Several of these fractions were stronger inhibitors than aspirin (Figure B.14).

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Black cohosh

Black cohosh (*Actea racemosa* and *Cimicifuga racemosa*) is related to the buttercup family, a perennial plant native to North America. Its botanical name was recently changed from *Cimicifuga racemosa* (L.) Nutt. to *Actea racemosa* (Ranunculaceae) (Compton et al., 1998a, b). Extracts prepared from its roots and rhizomes are standardized to 26-deoxyactein content, a member of a group of compounds known as saponins (Chen et al., 2001). It is used as an alternative to hormone-replacement therapy to treat hot flashes and other menopausal symptoms (Lieberman, 1998; Hardy, 2000). A randomized, double-blind, placebo-controlled study of 80 menopausal women treated with a black-cohosh extract was compared to a control of conjugated estrogens over a 12-week period (Stoll, 1987). A marked decrease in hot flashes was observed for women on black-cohosh extract (4.9 to 0.7 hot flashes/day) compared to either the control (5.1 to 3.1 hot flashes/day) or estrogen group (5.2 to 3.2 hot flashes/day). A later study also found a similar decrease in hot flashes was experienced by breast-cancer survivors treated with black cohosh or an antiestrogen (Jacobson et al., 2002). The American College of Obstetricians and Gynecologists (ACOG) suggest black cohosh may be helpful in the short term for women with vasomotor symptoms of menopause (ACOG, 2001). Burdette and coworkers (2002) showed methyl caffeate, ferulic acid, and caffeic acid were the primary antioxidants present in methanol extracts of black cohosh that scavenged oxygen radicals and prevented menadione-induced DNA damage.

Li and coworkers (2003) attempted to analyze caffeic-acid derivatives in black cohosh using liquid chromatography/tandem mass spectrometry. A number of derivatives were detected, with six identified as caffeic acid, ferulic acid, isoferulic acid, fukinolic acid, cimicifugic acid A, and cimicifugic acid. Novel compounds with dehydrofukiic acid groups were also reported for the first time in black cohosh. The bioactive properties of these compounds require extensive investigations.

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Black currant (*Ribes nigrum*)

see also Gamma Linolenic Acid (GLA) Black currant berries have a very dark coloration due to their content of anthocyanin pigments. They also contain large amounts of flavonoids, phenolic acids and proanthocyanidins. The seeds are also recognized for their content of γ -linolenic acid (GLA), an important polyunsaturated fatty acid, which has important health-related properties. GLA remains stable in the seed due to the presence of large amounts of antioxidants. The berries are used in beverages due to their high content of these antioxidants (Constantino et al., 1993). Lu and Foo (2002) confirmed the presence of four major anthocyanins based on rutosides and glucosides of delphinidin and cyanidin. They also identified for the first time aureisidin and 1-cinnamyl- β -D-glucoside in black currant. The importance of these anthocyanins is related to their antioxidant and pharmaceutical properties (Andersen et al., 1998; Constantino et al., 1992, 1993).

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Black pepper (*Piper nigrum*)

see also Piperine Black pepper is a common spice used in foods. It is rich in the alkaloid piperine, which is a member of a group of compounds based on the structure of vanillin, referred to as “vanilloids.” It has been shown previously to enhance the serum levels of drugs and nutrients in animals and humans (Bano et al., 1991; Majeed et al., 1996). Badmaev and coworkers (2000) showed that piperine significantly increased the plasma levels of coenzyme Q10 by almost a third compared to the placebo. This effect could be attributed to an earlier study on its thermonutrient activity (Badmaev et al., 1999).

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Black tea

Black tea is the fermented tea, which contains a group of yellow- to darkbrown-colored polyphenolic compounds formed during fermentation (Xiao et al., 1998). Theaflavins (TF) and thearubigins (TR) are the two major classes of polyphenols responsible for its color and taste. During fermentation, these pigments form a mixture of catechin dimers, trimers, or multipolymers, referred to as tea pigments (Nursten, 1997). Animal and clinical studies have demonstrated the ability of tea pigments to treat hypertension, decrease blood sugar, and prevent atherosclerosis and cancer (Morse et al., 1997; Ye, 1997). Tea pigments were also shown to increase superoxide dismutase (SOD) activity and decrease lipid-peroxidation levels in experimental animals (Li et al., 1998; Ren et al., 1998). Cadneri et al. (2000) showed that polyphenolic extracts from black tea was similar

to wine extracts in their ability to protect rats against AOM-induced colon carcinogenesis (Table B.12). Black-tea

TABLE B.12

Number of Adenomas or Cancers in the Colon/Rectum of AOM-Induced Rats Treated with Different Polyphenol Extracts

Group (n)	Tumors in the Colon-Rectum/ Rats Adenomas	Cancers
Controls (22)	1.72±1.31	0.82±1.00
Black tea (22)	1.00±1.15*	0.54±0.80
Green tea (22)	2.55±1.50	0.70±1.03
Wine extract (22)	1.09±1.30	0.54±0.74

Note: *Significantly different ($p<0.05$) from control.

Source: From Caderni et al., *Carcinogenesis*, 21:1965–1969, 2000. With permission.

extracts were far more effective than green-tea extracts in increasing apoptosis of the tumors. The anticarcinogenic properties of black-tea extracts were demonstrated by Shukla and Taneja (2002), who reported significant decreases in the number of diethylnitrosamine (DEN)-induced pulmonary tumors in Swiss albino mice fed 2 percent and 4 percent blacktea extracts. Yaping and coworkers (2003) recently showed that tea pigments had similar free-radical-scavenging abilities to tea polyphenols, which further supports their role in disease prevention.

A melanin-like pigment was isolated by Sava et al. (2001) from black tea leaves by alkaline extraction, acid hydrolysis, and precipitation. The isolated pigment had immunostimulating activity, suggesting possible health benefits. Significant antimutagenic effects were also reported by Gupta et al. (2002) for black tea and its polyphenols using the Ames Salmonella assays. Recent work by Besra et al. (2003) also demonstrated the antidiarrheal properties of a hot-water extract of black tea.

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Blueberries

Blueberries are rich sources of procyanidins and anthocyanins. Catechin and epicatechin were reported as monomers with (epi)catechin oligomer units exclusively singly linked (B-type) (Prior et al., 2001). Blueberries were among those fruit that strongly reduced the genotoxicity of 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP) in a dose-dependent manner in metabolically competent Chinese hamster-lung fibroblast V9 cells (Edenharder et al., 2002). Mazza and coworkers (2002) reported that 19 out of 25 anthocyanins, both intact glycosylated and possibly acylated forms, were absorbed by human subjects who consumed a high-fat diet together with a freeze-dried blueberry powder. The increase in serum anthocyanin levels correlated with an increase in serum antioxidant activity (ORAC) (Figure B.15).

Kay and Holub (2002) reported that consumption by healthy human subjects of a freeze-dried powder from wild blueberries

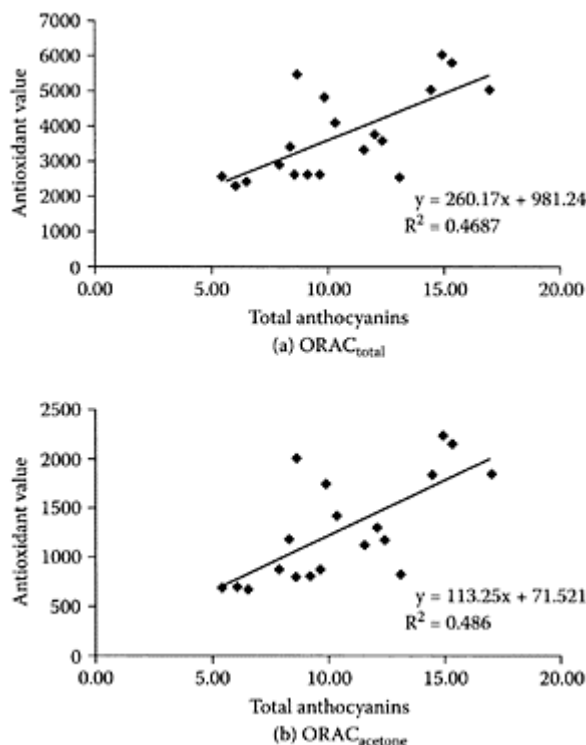


FIGURE B.15 Correlation between serum antioxidant capacity and concentration of serum total anthocyanins. Antioxidant value expressed as micromoles of Trolox equivalents per liter, and anthocyanins expressed (nanograms per milliliter of serum) as cyanidin 3-glucoside chloride. (From Mazza et al., *J. Agric. Food Chem.*, 50:7731–7737, 2002. With permission.)

(*Vaccinium angustifolium*), together with a high-fat meal, significantly increased serum antioxidant status (determined by ORAC and TAS assays) compared to control diets. This increase in blood-antioxidant status has been associated with decreased risk in atherosclerosis (Durak et al., 2001) and cancer (Ching et al., 2002).

A number of proanthocyanidin fractions were recently separated from wild-blueberry extracts by Schmidt et al. (2004). Of these, only the high-molecular-weight proanthocyanidin oligomers exhibited antiproliferation and antiadhesion properties. For

example, two fractions composed predominantly of four to eight linked oligomeric proanthocyanidins with average degrees of polymerization of 3.25 and 5.65 prevented adhesion of the organism responsible for urinary infections, *Escherichia coli*. However, only the latter fraction exhibited significant antiproliferation activity against human prostate and mouse liver-cancer cells.

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Borage oil

Borage oil is a high gamma-linolenic acid (GLA; C18:3n-6) oil extracted from borage seeds (*Borago officinalis* L.). The composition of the oil is shown in Table B.13. GLA accounts for almost 25 percent of the total fatty acids in borage oil. Mounting evidence points to GLA as a potent blood-pressure-lowering nutrient, making it a potential dietary intervention for hypertension (Das, 1995; Narce and Poisson, 1995; Engler et al., 1992). Engler and Engler (1998) found GLA-rich oils, such as

TABLE B.13**Typical Fatty-Acid Composition of Borage Oil**

Fatty Acid	Percent of Total Fatty Acids
C16:0	12.1
C18:0	3
C18:1	18.1
C18:2n-6	37.7
C18:3n-6	24.6
C18:3n-3	4.5
Total PUFA	66.7

Source: Adapted from Takahashi et al., *Comp. Biochem. Physiol.*, Part B, 127:213–222, 2000.

borage oil, increased the composition of GLA and dihomogamma-linolenic acid in the plasma, hepatic, and vascular tissue of spontaneously hypertensive rats. The changes in fatty-acid profiles brought about by GLA-enriched oils were attributed to its favorable blood-pressure-lowering effect.

Another role for GLA is its ability to attenuate body-fat accumulation in rats. Obese Zucker rats fed black currant oil containing 70 percent GLA were found to have lower bodyfat content compared with those animals fed soybean oil (Phinney et al., 1993). Takahashi and coworkers (2000) showed that GLA-rich borage oil reduced white adipose tissue weight compared to safflower oil by increasing gene expressions of the uncoupling protein 1 in brown adipose tissue.

Consumption of borage oil was also shown by Brosche and Platt (2000) to significantly and statistically improve skin function in the elderly. They reported a 34 percent reduction in itching, as well as in dry skin from 42 to 14 percent. Another benefit of borage oil is in the treatment of rheumatoid arthritis, due to its ability to decrease the tumor necrosis factor (TNF- α), a central tissue destructive mediator in rheumatoid arthritis (Belch and Hill, 2000). Kast (2001) reviewed double-blind studies suggesting borage oil was beneficial for treating rheumatoid arthritis. He proposed a mechanism whereby GLA in borage oil raised prostaglandin E levels, which in turn increased cAMP levels that suppressed TNF- α . He further cautioned against the use of nonsteroidal anti-inflammatory drugs, which would undermine the effects of borage oil.

Gadek and coworkers (1999) showed that enteral nutrition with special diets containing either EPA or GLA reduced the number of neutrophils in bronchoalveolar lavage fluid, as well as reducing pulmonary inflammation. This resulted in improved clinical outcomes in patients suffering from acute respiratory distress syndrome (ARDS). To explain the anti-inflammatory effects of EPA and GLA, Gillis and coworkers (2002) hypothesized this was due to induction of neutrophil apoptosis. Their studies showed that EPA and GLA, alone or in combination, triggered the induction of apoptosis and secondary necrosis in human promyelocytic HL-60 cells. Thus, inclusion of GLA and EPA could improve clinical outcomes in ARDS.

Using a double-blind, monocentric trial with parallel groups of healthy male volunteers between the ages of 18 and 30, Duriez et al. (1997) showed it was possible to provide oral supplements of borage oil (3 g/day) over six weeks without having any adverse effects on platelet aggregation.

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Bovine lactoferrin

see also Lactoferrin Lactoferrin, an iron-binding protein found in milk, also possesses bacteriocidal activity. A 25-residue peptide released from the aminoterminal region of bovine lactoferrin catalyzed at acidic pH by pepsin was shown to have potent bacteriocidal activity (Bellamy et al., 1992). Such a reaction can occur in the stomach, in which a stable lactoferricin B is released into the intestine (Kuwata et al., 1998a, b). The

intact peptide is extremely basic, with five arginine and three lysine residues. Lactoferrin appears to regulate immune and inflammatory responses by regulating the production of some cytokines, including interleukins and tumor necrosis factor- α (TNF- α) (Brock et al., 2000; Choe and Lee, 1999). Strom and coworkers (2001) examined the effects of charge and lipophilicity on the antibacterial activity of an undcapeptide (FKCRRWQWRMK) derived from bovine lactoferricin. All undcapeptides had Trp residues in positions 6 and 8 and Arg in positions 5 and 9 and were more effective against Gram-positive bacteria, such as *Staphylococcus aureus*, with a higher bacteriocidal effect against *Escherichia coli* than *Pseudomonas aeruginosa*.

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Bovine plasma

Only a small portion of blood taken from an animal after slaughter is used as emulsifiers, stabilizers, clarifiers, and as nutrients for foods. Interest in identification of bioactive peptides led to isolation of bovine blood plasma hydrolysates, including opioid peptides (Zhao et al., 1997), bradykinin-potentiating peptides (Piot et al., 1992), and several angiotensin 1-converting enzymes (ACE) (Hyun and Shin, 2000; Suetsuna, 1995). Janitha et al. (2002) reported the production of a number of bioactive peptides, following hydrolysis of defibrinated plasma (DBP), a by-product of meat-processing plants, with a microbial protease. Examination of the different protein hydrolysates, following various degrees of hydrolysis (DH), showed an increase in ACE inhibition accompanied an increase in DH. The highest inhibitory activity was found for the 42 percent DH hydrolysate. Peptides were separated by size-exclusion chromatography, and the fraction

with the greatest inhibitory activity contained peptides with GYP, HL(1), HPY, HPGH, L(1)F, SPY, and YPH sequences. Park and Hyun (2002) reported the production of bioactive peptides with antigenotoxic activity following enzymatic hydrolysis of bovine plasma proteins with several different proteases.

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Bowman-Birk protease inhibitor

The Bowman-Birk protease inhibitor (BBI), is a family of different forms and isoforms of natural polypeptide serine protease inhibitors of trypsin and chymotrypsin found in legume seeds, such as soybeans, chickpeas, and peanuts, and, to a lesser extent, in cereals, such as barley. Preclinical studies showed BBIs were effective suppressors of carcinogenesis both *in vivo* and *in vitro* (Kennedy, 1998). While the specific target(s) affected by BBIs have yet to be identified, indirect targets appear to be a modulation of superoxide anion radical production, oncogene levels, DNA repair, immune effects, and arachidonic-acid metabolism (Lippmann and Matrisian, 2000).

TABLE B.14

Clinical Response to BBI Concentrate with Respect to Dose Administered						
Dose ¹	Prog ²	NR ³	PR ⁴	CR ⁵	N	Response
200	0	7	1	0	8	12.5
533	0	7	3	1	11	36.36

800	2	5	2	0	9	22.22
1066	0	1	2	1	4	75
Total	2	20	8	2	32	31.25

¹CIU (chymotrypsin inhibitor units).

²Prog (progression), appearance of new lesions, or >50 percent increase in total lesion area.

³NR (no response), <50 percent reduction in total area of all lesions.

⁴PR (partial response), at least 50 percent reduction in total area of all lesions.

⁵CR, complete resolution of all lesions at completion of one month of BBI concentrate.

Source: From Armstrong et al., *Clin. Cancer. Res.*, 6:4684–691, 2000b. With permission.

Early work by von Hofe et al. (1991) noted soybean BBI effectively inhibited esophageal carcinogenesis induced by *N*-nitrosomethyl-benzylamine (NMBzA) in male Sprague-Dawley rats. A reduction of 45 percent in the frequency of papillomas and carcinomas was observed in rats receiving BBI in three tablets a week. The ability of BBI to prevent the development of malignancies has been demonstrated in a number of animal models (Kennedy, 1993). A phase I clinical trial conducted by Armstrong et al. (2000a) showed an oral dose of a BBI concentrate given to 24 patients suffering from oral leukoplakia was nontoxic. This was followed by a phase IIa clinical trial by Armstrong et al. (2000b) in which the same BBI concentrate was administered to 32 patients with oral leukoplakia. A 31 percent clinical response was observed, including two complete and eight partial, determined by pretreatment and posttreatment for individual and total lesion areas and analysis (Table B.14). The mean total lesion area decreased significantly ($p<0.004$) from 614 to 435 mm² following treatment with BBI concentrate with a linear dose-response relationship observed. The absence of toxicity combined with a dose-dependent decrease in oral leukoplakia area will require further randomized clinical trials to determine the efficacy of BBI concentrate in treating this condition.

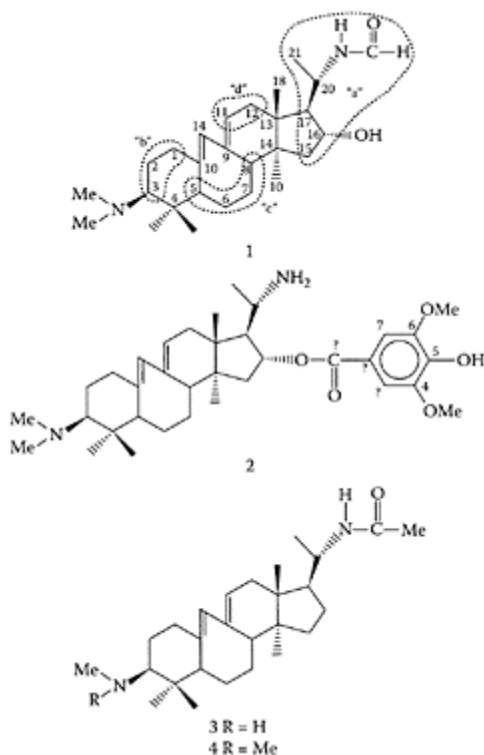
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Boxwood (*Buxus sempervirens*)

Boxwood is a popular woody, ornamental plant grown throughout Europe and North America. In folk



SCHEME B.9 Structure of four new alkaloids isolated from *Buxus sempervirens*. (From Loru et al., *Phytochemistry*, 54:951–957, 2000. With permission).

medicine, extracts from *Buxus* are used to cure different diseases, including the treatment of HIV infections (Valmet, 1983; Durrant et al., 1996, 1998). It is a rich source of steroidal alkaloids, with four new alkaloids extracted from its leaves by Loru and coworkers (2000). Some of these alkaloids may be responsible for some of the health-related properties attributed to boxwood (Scheme B.9).

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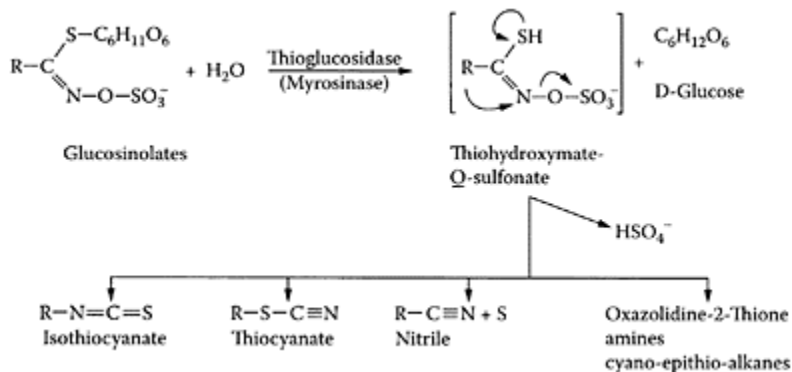
Brassica vegetables

see also Crucifera Brassica vegetables are among the most frequently consumed vegetables around the world (Lange et al., 1992a, b). They include white cabbage, red cabbage, broccoli, cauliflower, Brussels sprouts, and Savoy cabbage, as well as rape and mustard. They all contain glucosinolates, which undergo degradation to isothiocyanates, indoles, and nitriles (Scheme B.10). The chemopreventive properties of these vegetables are related to the ability of their bioactive components to inhibit phase I enzymes and to activate phase II enzymes, such as glutathione S-transferase (GST).

Brassica vegetables, such as broccoli, cauliflower, Brussels sprouts, and kale, have been reported to exhibit strong anticancer properties. A diet rich in Brussels sprouts decreased urinary excretion of 8-oxidG, indicative of DNA damage (Verhagen et al., 1997), while a low risk of lung cancer in Chinese men was associated with a high urinary excretion of isothiocyanates (London et al., 2000). One explanation for the decreased cancer risk associated with vegetable intake is related to induction or inhibition of biotransformation enzymes. Lampe and coworkers (2000) found Brassica vegetables increased while apiceous vegetables decreased cytochrome P450 1A2 in human subjects. Steinkellner et al. (2001) showed that it was the degradation compounds of glucosinolates in Brassica vegetables that were responsible for the protective effect against carcinogens. For example, indoles and isothiocyanates attenuated the carcinogenic effects of polycyclic aromatic hydrocarbons (PAHs), as well as against heterocyclic amines.

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SCHEME B.10 Chemical structures of glucosinolates and their breakdown products following enzymatic hydrolysis by myrosinase. (Adapted from Pessina et al. (1990) by Steinkellner et al., *Mutat. Res.*, 480–481:285–297, 2001. With permission.)

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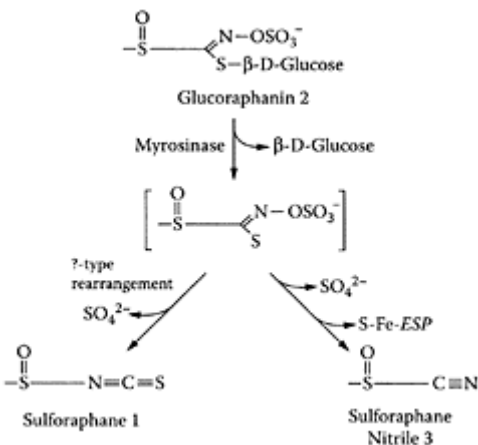
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Broccoli

Consumption of Brassica vegetables, such as broccoli, leads to excretion of isothiocyanates (ITCs) in the urine. These compounds are produced by enzymic hydrolysis of intact thioglucoside conjugates or glucosinolates and may have a role as cancer chemopreventative agents (Conaway et al., 2002). The major glucosinolate in broccoli, glucoraphanin, is hydrolyzed by myrosinase to sulforaphane or sulforaphane nitrile (Scheme B.11). Matusheski and Jeffery (2001) compared the biactivity of these metabolites in mouse hepatoma cells.

Sulforaphane proved to be the most potent in inducing phase II detoxification enzymes and had



SCHEME B.11 Hydrolysis of glucoraphanin to sulforaphanes. (From Matusheski and Jeffery, *J. Agric. Food Chem.*, 49:5743–5749, 2001. With permission.)

TABLE B.15

Effect of Diets Containing 20 Percent Prehydrolyzed Broccoli (Broccoli-HP), 20 Percent Unhydrolyzed Broccoli with Intact Glucosinolates (Broccoli-GS), or Purified Sulforaphane (5.0 mmol of SFG/kg of Diet) Compared to a Control-

Modified, AIN-76 B-40 Diet (C) on Hepatic and Colonic Mucosal Quinone Reductase (QR) of Rats Fed These Diets for Five Days²

Diet	Colonic QR Activity ² (mmol of DPIP/min/mg of Protein)	Hepatic QR Activity ² (mmol of DPIP/min/mg of Protein)
	Colonic QR Activity ²	Hepatic QR Activity ²
C	122.1±17.4a	68.3±6.1a
Broccoli-HP	396.6±29.6b	77.3±7.4ab
Broccoli-GS	543.7±33.9c	94.4±8.7b
SF	559.0±43.2c	97.3±6.5b

¹Values shown are means±SE, n=5. Different letters within a column indicate values that differ significantly ($p \leq 0.05$).

²QR activity measured using 2,6-dichlorophenolindophenol (DPIP) as the substrate.

Source: Adapted from Keck et al., *J. Agric. Food Chem.*, 51:3320–3327, 2003.

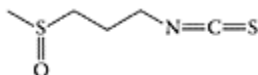
much greater potential as a chemoprotective agent than the corresponding nitrile. Keck et al. (2003) showed intact broccoli glucosinolates (Broccoli-GS) enhanced quinone reductase (QR) in the liver and colon of Fischer 344 rats far more than when fed hydrolyzed broccoli (Broccoli-HP) (Table B.15). There were no significant differences in the colonic or hepatic QR activity of rats fed a purified sulforaphane (SF) diet or the intact Broccoli-GS diet. They suggested that urinary sulforaphane conjugate of mercapturic acid was a useful biomarker for assessing the effects of dietary broccoli on QR induction in the liver and colon and could be extrapolated to measure the relative cancer prevention effects of broccoli. Based on the oxygen-radical absorbance capacity (ORAC) assay, broccoli was shown to be seventh in antioxidant capacity after kale, Brussels sprouts, alfalfa sprout, beets, and spinach broccoli (Cao et al., 1996). However, using linoleic-acid emulsions and phospholipid bilayers, Azuma and coworkers (1999) found broccoli (*Brassica oleraceae* var *italica*) exhibited the greatest antioxidant activity compared to 25 vegetable extracts (Wallig et al., 1999). The many antioxidants present in broccoli include carotenoids, tocopherols, ascorbic acid, and flavonoids (Kurilich et al., 1999; Plumb et al., 1997). Using the ORAC assay, Kurilich et al. (2002) showed considerable variability in the antioxidant capacity of eight broccoli genotypes. They were unable to explain the variability based on ascorbic acid and flavonoid content of the hydrophilic extracts suggesting the presence of other antioxidants or synergism. The carotenoids in the lipophilic extracts correlated with antioxidant capacity and accounted for the majority of the variability in this fraction.

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Broccoli sprouts

Research conducted at Johns Hopkins University School of Medicine showed that broccoli sprouts contain from 20 to 50 times higher levels of sulforaphane glucosinolates than adult cooked broccoli and



Sulforaphane. (From Konwinski et al., *Toxicol. Lett.*, 153:343–355, 2004. With permission.)

could provide better anticancer protection (Nestle, 1998). Previous studies by Fahey et al. (1997) showed that broccoli sprouts were rich in enzyme inducers that protect against carcinogenesis. For example, broccoli contains large amounts of isothiocyanates, sulforaphane, or 4methyl-sulfinyl-butyl isothiocyanate, that are potent inducers of phase II enzymes. Isothiocyanates occur naturally as thioglucoside conjugates and appear to inhibit the development of cancerous tumors. Chung et al. (2000) confirmed the ability of

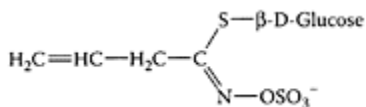
sulforaphane and phenylethyl isothiocyanate to inhibit the development of colonic aberrant crypt foci during the initiation period in experimental male rats treated with azoxymethane (AOM), an initiator of colon cancer. Based on their observations, Fahey and Talalay (2001) patented their discovery for the development of cancer chemoprotective food products based on broccoli sprouts.

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Brussels sprouts

Brussels sprouts (*Brassica oleracea* var. *gemmifera*) are particularly rich in the glucosinolate sinigrin. Sinigrin is hydrolyzed by myrosinase to allyl isothiocyanate (AITC), which was shown to induce glutathione



Sinigrin structure. (From Jen et al., *J. Chromatogr.*, A., 912:363–368, 2001. With permission.)

S-transferase activity in the liver and small intestine of rats (Bogaards et al., 1990). Musk and Johnson (1993) found that AITC selectively induced cell death in the undifferentiated phenotype of the HT29 human cell tumor cell line. Smith et al. (1998) reported that ingestion of sinigrin inhibited dimethylhydrazine-induced aberrant crypt foci, as well as induced apoptosis in the rat colon. The ability of AITC to act as a suppressor of colorectal carcinogenesis was further investigated by Smith and coworkers (2003). Freeze-dried raw and microwave-cooked Brussels sprouts containing high levels of glucosinolates significantly enhanced apoptosis and reduced mitosis in 1,2-

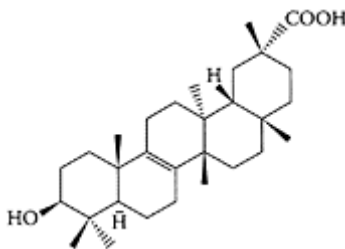
dimethylhydrazine (DMH)-induced colonic mucosal crypts. The absence of any effect in blanched-sprout tissue was attributed to the inactivation of myrosinase and the presence of only intact glucosinolates. This study confirmed the importance of glucosinolate degradation products in affecting cell proliferation and apoptosis.

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Bryonolic acid

Bryonolic acid is a multiflorane compound found in saffron as the p-aminobenzoate derivative. In his discussion of medicinal plants, Thatte et al. (2000) suggested compounds, such as bryonolic acid, induced programmed cell death arresting the proliferation of cancerous cell lines. Two novel multiflorane p-aminobenzoates were detected by Appendino and coworkers (2000) in zucchini seeds, while bryonolic acid was the sole multiflorane constituent found in zucchini sprouts.



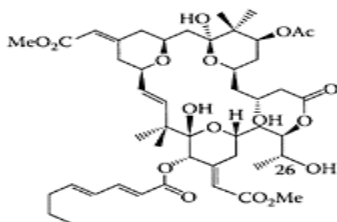
Bryonolic acid. (Adapted from from Appendino et al., *Fitoterapia*, 71:258–263, 2000.)

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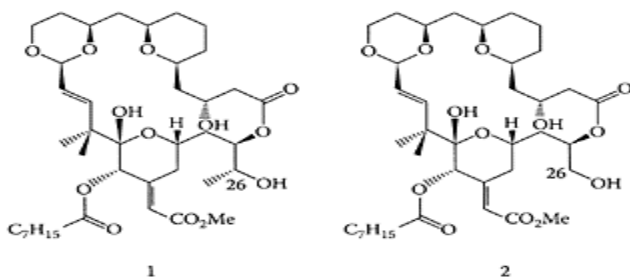
Bryostatins

Bryostatins, a group of marine macrocyclic lactones with a unique polyacetate backbone, have considerable potential as chemopreventive agents (Petite, 1996). Their low toxicity combined with their antineoplastic activity has made bryostatins ideal for treating cancer. Bryostatin 1, first isolated and characterized in 1982, is recognized for its immune stimulation, growth inhibition, induction of differentiation, and enhancement of cytotoxicity of other drugs directed at target cells (Watters and Parsons, 1999).



Bryostatin 1. (Baryza et al., *Chem. Biol.*, 11:1261–1267, 2004. With permission.)

Studies on bryostatins have focused on their interaction with enzymes and cell lines or on



SCHEME B.12 Structures of analogs 1 and 2. (From Baryza et al., *Chem.*

Biol., 11:1261–1267, 2004. With permission.)

how these enzyme activities or cellular events affect apoptosis. For example, the effect of bryostatin 1 on protein kinase C isoenzymes has been studied extensively. This family of 12 isoenzymes plays a central role in cell signaling and other processes and is activated by bryostatin 1, phorbol esters (a group of tumor promoters), and diacylglycerol. Hennings et al. (1987) showed bryostatin 1 inhibited tumor promotion by phorbol esters in SENCAR mouse skin.

Preclinical trials to investigate bryostatin 1 as an anticancer drug showed it inhibited the growth of rabbit papillomas in a dose-dependent manner but did not provide a cure (Bodily et al., 1999). Other studies showed that bryostatin 1, in combination with anticancer drugs, proved more effective. For example, a cure was reported for WSU-CLL-bearing SCID mice (5/5) using a combination of auristatin PE followed by bryostatin every second day over a six-day period (Mohammed et al., 1998). A phase II trial by Nezhat et al. (2004) found a combination of bryostatin 1 and the drug cisplatin ineffective in patients with advanced-stage or recurrent cervical cancer. However, several analogs (analog 1 and 2) of bryostatin 1 were later shown by Baryza and coworkers (2004) to be 50 times more potent than bryostatin at inducing translocation of PKC δ -GFF from the cytosol of rat basophilic leukemia (RBL) cells, suggesting great potential in cancer therapy (Scheme B.12). A review on bryostatins by Mutter and Wills (2000) is strongly recommended.

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Buckwheat

Buckwheat is a pseudocereal grown in North America, including Western Canada. The protein in buckwheat was shown by Kayashita and coworkers (1997) to lower plasma cholesterol and raise fecal neutral sterols in cholesterol-fed rats because of its low digestibility. In addition, buckwheat protein was found to retard the ability of 7,12-dimethylbenzyl [a] anthracene-induced mammary carcinogenesis in rats by lowering serum estradiol. The ability of buckwheat protein to suppress plasma cholesterol in rats fed a cholesterol-free diet was shown by Tomotake et al. (2001) to be stronger than a soybean protein isolate. The effect was attributed to the enhanced excretion of fecal neutral and acidic steroids. Yokozawa et al. (2001) reported that an aqueous extract from buckwheat ameliorated renal injury in rats induced by ischemia-reperfusion. The buckwheat extract also protected cultured proximal tubule cells subjected to hypoxia-reoxygenation, which was attributed to preventing oxygen free radicals from attacking the cell membranes. Earlier work by Lee et al. (1998) reported antioxidant and free-radical-scavenging activities among buckwheat-seed components. Holasova et al. (2002) showed the antioxidant activity of buckwheat seeds was higher than those of oats, barley, and buckwheat straws and hulls. The antioxidant activity resided primarily with the methanol-soluble components.

The hypoglycemic effects of consuming buckwheat flour or biscuits containing buckwheat flour in patients with diabetes was first reported in 1992 by several researchers (Lu et al., 1992; Wang et al., 1992). Kawa and coworkers (2003) recently showed that a single, oral dose of buckwheat concentrate significantly lowered elevated serum-glucose concentrations in streptozotocin-diabetic rats by 12–19 percent at 90 and 120 minutes after administration (Figure B.16). The active component in buckwheat responsible for the glucose-lowering effect appeared to be *D-chiro*-inositol, which is present at 0.2 percent in the concentrate. Fonteles et al. (2000) reported that a single dose of intragastric *D-chiro*-inositol (10 mg/kg) fed to streptozotocin-treated rats resulted in a 30–40 percent decrease in plasma-glucose concentrations. Buckwheat concentrate, a good source of

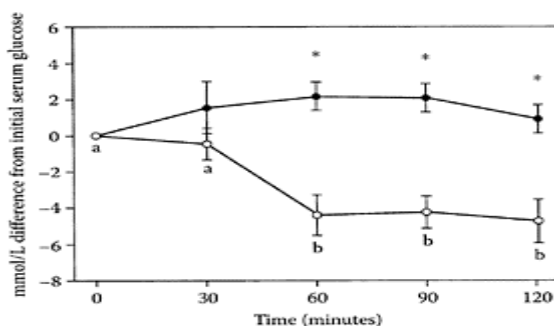


FIGURE B.16 Effect of low-dose buckwheat concentrate (10 mg of D-

chiro-inositol/kg of body weight) or placebo given to STZ rats in the fed state on serum-glucose concentration. Data are expressed as the mmol/L difference from initial serum glucose concentrations (28.4 ± 0.95 mmol/L) for the placebo low-dose (, n=9) and the low-dose buckwheat concentrate (, n=8) groups. Asterisks (*) indicate differences ($p < 0.001$) between placebo-treated and buckwheat-treated rats. Data points with different letters indicate differences ($p < 0.01$) within a group, determined by Duncan's multiple range. (From Kawa et al., *J. Agric. Food Chem.*, 51:7287–7291, 2003. With permission.)

d-*chiro*-inositol, could be beneficial for the treatment of diabetes.

A statistically significant correlation was observed between total phenolics and rutin and antioxidant activity of buckwheat. Steadman et al. (2000, 2001a) reported buckwheat bran was a good source of protein, lipid and dietary fiber, fagopyritols, d-*chiro*-mositol, and other soluble carbohydrates. Steadman and coworkers (2001b) cautioned against the use of buckwheat bran for medicinal purposes because of the high levels of phytate and tannin present. Li and coworkers (2002) reported the production of peptides from buckwheat protein that inhibited angiotensin 1-converting enzymes, which lowered the systolic pressure in hypertensive rats. While the intact protein had some ACE inhibitory activity, it was enhanced substantially by hydrolysis with chymotrypsin and trypsin. This effect was not exhibited by rutin. A recent study by Prestamo et al. (2003) showed buckwheat acted as a prebiotic by increasing lactic-acid bacteria while decreasing mesophilic bacteria in the intestine of rats.

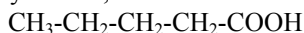
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Butyric acid

Butyric acid, a short-chain fatty acid, is a by-product of bacterial fermentation of dietary fiber. In addition to making the fecal pH more acid, short-chain fatty acids, such as butyric acid, decrease the activity of bacterial



7 α -dehydroxylase, which converts bile acid from primary to secondary (Hill, 1975), a cancer promoter. Butyric acid appears to be responsible for the beneficial effect of fiber on bowel cancer (Riggs and coworkers, 1977). *In vivo* and *in vitro* studies with rats showed butyric acid acts as a potent anti-inflammatory agent (Andoh et al., 1999) while another study showed it induced apoptosis in myeloid leukemia (HL-60) cell lines (Celabresse et al., 1993). Abrahamse and coworkers (1999) found butyrate reduced DNA damage induced by hydrogen peroxide in rat colon cells, pointing to butyrate having anticarcinogenic effects *via* its antioxidant properties. Rosignoli et al. (2001) confirmed butyrate's ability to reduce H₂O₂-induced DNA damage in colon cells, although the mechanism of action still remains unknown. Sodium butyrate was also shown by Sasahara and coworkers (2002) to inhibit the growth of colon cancer by suppressing expression of inducible nitric-oxide synthase (iNOS) involving mechanisms independent from histone acetylation. An oral butyrate derivative, tributyrin, was reported by Clarke et al. (2001) to be a potent inhibitor of colorectal cancer by inducing apoptosis through activation of caspase-3 activity. Chethankumar and coworkers (2002) reported that butyric acid that supplemented high-fiber diets fed to streptozotocin-induced diabetic rats slowed down the diabetic process by inhibiting intestinal and renal disaccharidases, slowing down the release of glucose and its absorption.

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C

Cabbage

see also Brassica and Crucifera The antioxidant and antiproliferative activities of 10 common vegetables (broccoli, spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, and celery) were recently studied by Chu and coworkers (2002). The phenolic content and antioxidant activity of cabbage fell in the middle, while antiproliferative activity, using HepG(2) human liver cells, was highest in spinach, followed by cabbage. Thus, cabbage had the second-highest bioactivity index (BI) suggested as an alternative biomarker for future dietary cancer-prevention studies.

Bresnick and coworkers (1990) reported that a diet containing cabbage significantly decreased the incidence of mammary cancer in female Sprague-Dawley rats injected with a carcinogen, *N*-methyl-*N*-nitrosourea (MNU). Later work by Mehta et al. (1995) reported that a synthetic brassinin [3-(*S*-methyldithiocarbamoyl)aminomethylindole], a phytoalexin first identified in cabbage, inhibited 7,12-dimethyl-benz [a] anthracene (DMBA) induction of mouse skin tumors.

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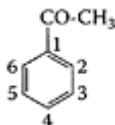
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Cacao

see Cocoa

Caesalpinia ferrea

The fruit of *Caesalpinia ferrea* or Juca, a leguminous tree in northern and northeastern regions of Brazil, was reported to have analgesic and anti-inflammatory properties (Carvalho et al., 1996). In addition, it was also used to treat diabetes (Balbach, 1972) and coughs and injuries (Hashimoto, 1996). The popular use of aqueous extracts of these fruit to treat cancer led to an investigation of its antitumor properties by Nakamura and coworkers (2002) using the *in vitro* Epstein-Barr virus early-antigen (EBV-EA) screening test. They identified the active constituents in *Caesalpinia ferrea* fruits responsible for antitumor effects as gallic acid and methylgallate. A total of 49 related compounds were also identified, of which three acetophenone derivatives, 2,6-dihydroxyacetophenone, 2,3,4-trihydroxyacetophenone, and 2,4,6-trihydroxyacetophenone, proved to be the most potent activity.



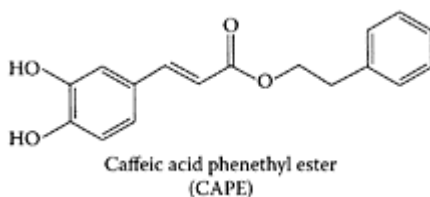
Acetophenone structure. (From Nakamura et al., *Cancer Lett.*, 177:119–124, 2002.)

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Caffeic acid

Caffeic is one of the phenolic compounds in fruits and vegetables with strong antioxidant properties. Uz and coworkers (2002) showed that caffeic acid phenethyl ester (CAPE), a new antioxidant and anti-inflammatory agent, had a protective role on rat testicular tissue from reactive-oxygen species produced by testicular artery occlusion. In propolis (honeybee resin), caffeic acid is also present as



(From Celli et al., *J. Chromatogr. B.*, 810:129–136, 2004.)

the phenylethyl ester (Michaulart et al, 1999). Like caffeic acid, CAPE was shown in both *in vivo* and *in vitro* studies to be an anti-inflammatory compound (Huang et al., 1996; Michaulart et al., 1999; Orban et al., 2000). The anti-inflammatory properties of CAPE were attributed by Natarajan and coworkers (1996) to its inhibitory action on the transcription factor nuclear factor-B (NF-B). CAPE was also reported to induce apoptosis (Chiao et al., 1995; Chen et al., 2001). Fitzpatrick and coworkers (2001) showed CAPE inhibited NF-B and cytokine production in cell types for inflammatory-bowel disease (IBD). Lee and coworkers (2000) showed that synthetic caffeic phenylethyl ester-like compounds were cytotoxic on oral submucous fibroblasts, neck metastasis of Gigiva carcinoma, and tongue squamous-cell carcinoma cells. Further work was proposed to establish the efficacy of CAPE-like compounds as chemopreventive agents against oral cancer.

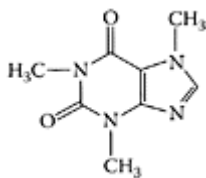
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Caffeine

Caffeine, 1,3,7-trimethylxanthine, consumed in such drinks as coffee and tea, is well-known for its biochemical and physiological activities. In recent years, evidence has accrued that caffeine can inhibit carcinogenesis



Structure of caffeine. (From Nafisi et al., *J. Mol. Struct.*, 705:35–39, 2004. With permission.)

in mice and rat lungs exposed to a nicotinederived carcinogen (Chung, 1999; Chung et al., 1998), in mice skin exposed to ultraviolet light (Lu et al., 2001), and in rat stomachs exposed to a carcinogen and sodium chloride (Nishikawa et al., 1995). In contrast, however, no inhibition was observed when mammary glands were exposed to specific carcinogens in the presence of caffeine (VanderPloeg et al., 1991). Hagiwara and coworkers (1999) reported caffeine exerted a chemoprotective action against the carcinogen 2-amino-1-methyl-6-phenyl-imidazo [4,5-*b*]pyridine (PhIP) in female F344 rats for 54 weeks by significantly reducing mammary-gland tumor formation. Takeshita et al. (2003) were unable to explain how caffeine differentially modifies PhIP-induced

colon and mammary carcinogenesis. The only parameter they found contributing to the elevation of colon carcinogenesis was elevation in PhIP-DNA adduct formation. Caffeine at a concentration of 2 mM enhanced the radiosensitivity of two rat yolk-sac cell lines with a mutant-type p53 by inducing apoptosis through a p53-independent pathway (Higuchi et al., 2000). Ito et al. (2003) also showed caffeine-induced G₂/M phase cell-cycle arrest in NB4 promyelocytic leukemia cells and apoptosis via activation of p53 by a novel pathway.

Kitamoto et al. (2003) reported that caffeine, combined with paclitaxel, a naturally occurring chemotherapeutic agent from the bark of the Western yew, suppressed cell proliferation in a dose-dependent manner. Examination of the

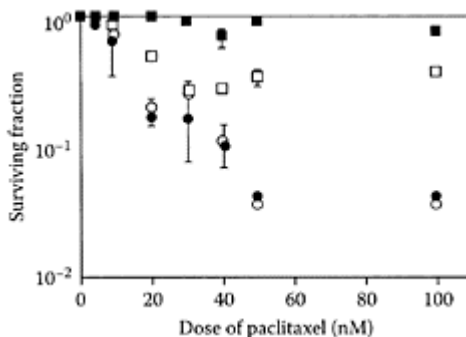


FIGURE C.17 Dose-response of A549 on paclitaxel alone, paclitaxel with 1, 5, and 20 mM of caffeine for 24 h, paclitaxel alone, (○), paclitaxel+caffeine 1.0 mM, (●), paclitaxel+caffeine 5.0 mM, (□), paclitaxel+caffeine 20 mM (■). Bar shows \pm SE where these exceed the size of the symbol. (From Kitamoto et al., *Cancer Lett.*, 191:101–107, 2003. With permission.)

dose responses of paclitaxel alone and in combination with caffeine on the survival of a human lung adenocarcinoma cell line, A549, is shown in Figure C.17. The cell-killing effect of paclitaxel increased in a dose-response manner up to a maximum of 50 nM, with no further improvement at 100 nM. Combining with 5 mM caffeine, however, reduced the cytotoxicity of paclitaxel, which was further dramatically suppressed in the presence of 20 mM caffeine. These researchers showed that in the cell-cycle analysis, caffeine caused early G1 accumulation, while paclitaxel caused an early increase in G2-M and a decrease in G1. These effects suggested that while cell-modifying agents, like caffeine,

can diminish the cytotoxic effects of paclitaxel, caution should be exercised in combining these substances.

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Calcium

Because of its importance in bone formation, particularly in relation to osteoporosis, calcium is now added to such beverages as orange juice. In addition, calcium also appears

to exert cancer-preventive properties. Enhanced cell proliferation, an early biological event in the carcinogenesis process, combined with an abnormal distribution of proliferating cells in the colon, was evident in animals exposed to carcinogens and in humans with a high risk for colon cancer. Studies with human subjects have shown that calcium supplementation may reduce epithelial-cell proliferation, particularly in patients with a high risk for colon cancer (Wargovich et al., 1992; Bostick et al., 1993; O'Sullivan et al., 1993). Karkare et al. (1990) reported that supplemental calcium, relative to the standard concentration of 5.07 g/kg diet, decreased colon-tumor incidence in rats, although a lower concentration of 2.0 g/kg also reduced the incidence. However, Whitfield et al. (1995) cautioned that increasing calcium in the diet could actually promote colon cancer. Nevertheless, there is a large body of scientific evidence that increasing dietary calcium above normal levels may reduce colon cancer (Wargovich et al., 1990; Bostick et al., 1993; O'Sullivan et al., 1993) and that this risk could also be reduced by decreasing calcium below this level (Karkare et al., 1990).

Li and coworkers (1998) showed that both low (0.5 and 1.0 g/kg) and high (10.0 and 15.0 g/kg) levels of calcium reduced the yield of azoxymethane (AOM)-induced aberrant crypt foci (ACF) in rat colons, relative to 5.0 g/kg of calcium (Figure C.18). A reduction in the yield of ACF with two or more crypts suggested that calcium levels above and below the standard level of 5.0 g/kg inhibited the promotion/progression of foci into tumors. A decrease in cell proliferation was also observed in the presence of low and high calcium levels by a reduction in both the PCNA-labeling index and the size of the PCNA-proliferative. Beaty and coworkers (1993) reported a nonstatistically significant reduction in tumor incidence of 1,2-dimethylhydrazine-induced colon carcinogenesis in rats fed high-fat diets containing vitamin D and calcium. Using diets containing 5000 and 15,000 ppm calcium with and without the presence of

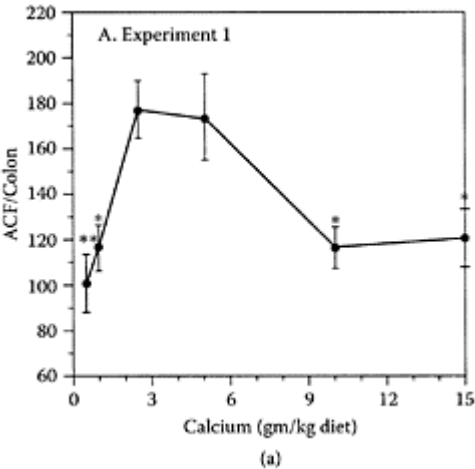


FIGURE C.18 Effect of calcium on the yield of AOM/induced ACF. Results of means±SE treatment group

containing 12 rats. Statistically different results for the treatment group administered 5.0 g/kg as calcium are labeled, respectively, $*p<0.05$ and $**p<0.01$. (From Li et al., *Cancer Lett.*, 124:39–46, 1998. With permission.)

vitamin D and acetylsalicylic acid (ASA), Molck et al. (2002) found calcium levels affected ACF and tumor development differently. The number of ACF decreased with the higher calcium concentration, while the number of tumor-bearing animals increased with increasing calcium, either directly or indirectly, by adding vitamin D₃ together with ASA. This study showed calcium was a strong modulator of ACF and tumor development and masked the effect of vitamin D and ASA. Low calcium levels increased both the development of advanced ACF, as well as tended to increase tumor incidence. The latter can be avoided by adding vitamin D and ASA. These findings suggest that a high calcium intake may interact with other dietary or therapeutic components. These researchers cautioned against increasing calcium levels above recommended levels, as it could give initiated cells growth advantages compared to normal cells.

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Calendula officinalis L.

Calendula officinalis L. (Marigold), an annual herb found in the Mediterranean region, is grown for ornamental and medicinal purposes in Europe and North America. Many properties have been associated with tinctures and decoctions from its flowers, including anti-inflammatory, antitumoral, and analgesic (Duke, 1991). Cytotoxic effects were reported for extracts from its leaves, flowers, and whole plant against three cells lines from Ehrlich carcinoma. One of these extracts, rich in saponins, exhibited antitumoral activity in an *in vivo* Ehrlich mouse carcinoma model (Boucaud-Maitre et al., 1988). Ramos and coworkers (1998) found a 60 percent aqueous-alcohol extract from *Calendula* flowers was not mutagenic in the Ames test but did report a genotoxic effect in the mitotic segregation assay of the heterozygous diploid D-30 of *Aspergillus nidulans*. This fraction was shown to contain a terpene lactone, tentatively identified as (–) oli-olide (calendin), together with acyclic hydrocarbons. Two polar (aqueous and aqueous-alcohol) extracts from *C. officinalis* flowers were shown by Perez-Carreón et al. (2002) to be antigenotoxic at low concentrations by protecting rat-liver cell cultures from diethylnitrosamine (DEN) treatment. The opposite was observed at high concentrations, in which genotoxic effects were observed by the same extracts containing flavonols. These researchers pointed out that the concentration effect of these extracts must be clarified if these polyphenols are to be considered for therapeutic treatment.

Hamburger and coworkers (2003) developed a relatively simple, efficient preparative method for purifying the major anti-inflammatory triterpenoid esters from *Calendula* flower heads. The major compounds identified were faradiol esters, while the minor triterpenoid esters included maniladiol 3-*O*-laurate and myristate.

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Cane sugar

The pressed juice from sugar cane (*Saccharum officinarum* L.) is used in Japan for the production of *Kokuto*. Previous studies isolated and characterized a number of phenolic compounds in *Kokuto* exhibiting antioxidant activity (Nakasone et al., 1996; Takara et al., 2000). Takara and coworkers (2002) recently isolated seven new phenolic glycosides, together with two known phenolic glycosides. Using the 2-deoxyribose oxidation method, all of these compounds exhibited antioxidant activity.

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Canola

Canola oil, the major edible in Canada, is recognized as a well-balanced oil, low in saturates, high in monounsaturates, and a good source of polyunsaturated acids (Table C.16). It is particularly low in saturated fatty acids (<7.0 percent), accounting for half the level found in olive or soybean oil. In addition, the high level of monounsaturated fatty acids in canola oil provides possible protection against oxidation of LDL. This is important as uptake of LDL and formation of fatty streaks in the intima of blood vessels, an early lesion of atherosclerosis, is characterized by enhanced oxidation of LDL (Steinberg et al., 1989; Parathasarathy and Rankin, 1992). Canola oil is high in linoleic acid (>20 percent), a member of the ω -6 family of essential fatty acids that are precursors of arachidonic acid and eicosanoids, hormone-like substances involved in many functions, such as blood clotting to immune responses. Canola oil is one of the few

TABLE C.16

Fatty-Acid Composition of Canola Oil

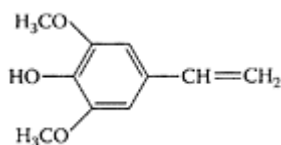
Fatty Acid	(%)
C14:0	0.1
C16:0	3.6
C18:0	1.5
C20:0	0.6
C22:0	0.3
C24:0	0.2
Saturated	6.3
C16:1	0.2
C18:1	61.6
C20:1	1.4
C22:1	0.2
Monounsaturated	62.4
C18:2n-6	21.7
C18:3n-3	9.6
Polyunsaturated	31.3

Source: Adapted from Przybylski et al., 2004. With permission.

oils high in α -linolenic acid (>9 percent), an essential ω -3 fatty acid that is a precursor of docosahexaenoic acid (C22:6 ω -3), a major component of lipids in the brain and retina of the eye, and eicosapentaenoic acid (C22:5 ω -3), a precursor of another group of eicosanoids. There is a favorable balance in canola oil of 1:2 for the ratio of α -linolenic acid (10 percent) and linoleic acid (21.7 percent).

Animal studies have shown that diets high in polyunsaturated and monounsaturated fatty acids promote reduced fat accumulation compared to diets high in saturated fatty acids. Ellis and coworkers (2002) confirmed the ability of canola oil (high in monounsaturated fatty acids) to reduce fat deposition in growing female rats compared to corn oil (high in polyunsaturated fatty acids) and coconut oil (high in saturated fatty acids). In high-fat diets (40 percent calories), rats fed corn oil had a much larger fat-cell size compared to either canola or coconut oils, although the number of fat cells was much greater in coconut-oil-fed animals than the other oils. On the low-fat diet (6 percent calories), canola oil had a definite advantage over corn oil, as the animals had a lower body-weight gain. This study demonstrated the benefits of a diet high in monounsaturated fatty acids because of its ability to reduce adiposity and plasma lipids.

Wakamatsu (2001) isolated a potent antioxidant in crude canola oil, which was subsequently identified as 4-vinyl-2,6-dimethoxyphenol, or canolol. Recent work by Kuwahara



Canolol. (From Kuwahara et al., *J. Agric. Food Chem.*, 52:4380–4387, 2004.)

et al. (2004) found canolol prevented apoptosis in mammalian cells induced by oxidative stress. Canolol proved toxic to cultured human colon cancer cells *in vitro* when present at 560 μ M (Figure C.19A) as well as prevented apoptosis induced by oxidative stress by *tert-butyl hydroperoxide* (t-BuOOH) (Figure C.19B).

In addition, canolol also prevented DNA-strand breakage by peroxynitrite in a dose-dependent manner. The chemopreventive effects of canolol indicate its potential as a new nutraceutical.

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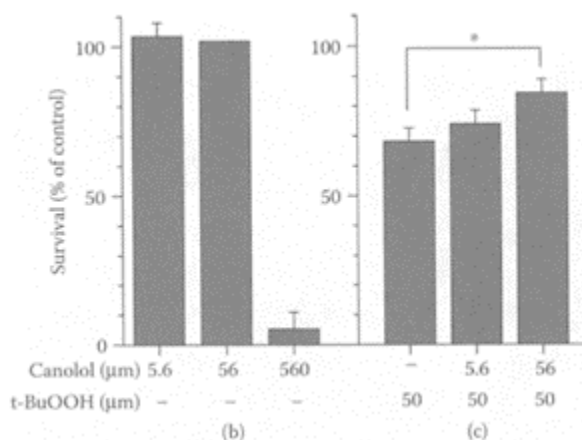


FIGURE C.19 (a,b) Inhibition of t-BOOH-induced cytotoxicity in mammalian cells by canolol [values are means (n=6 wells); bars indicate SE; * $p<0.05$). (From Kuwahara et al., *J. Agric. Food Chem.*, 52:4380–4387, 2004. With permission.)

Steinberg, D., Parthasarathy, S., Carew, T.E., Khoo, J.C., and Witztum, J.L., *N. Engl. J. Med.*, 320:915– 1989.

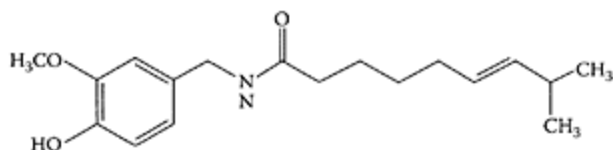
Wakamutsa, D., Isolation and identification of radical scavenging compound, canolol, in canola oil, Master's thesis, Graduate School of Natural Science, Kumamoto University, Kumamoto City, Japan, 2001, pp. 1–48.

Capsaicin

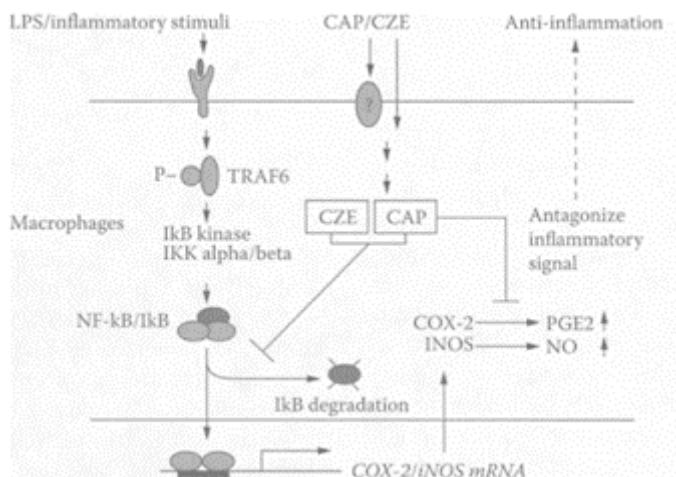
Capsaicin (*trans*-8-*N*-vamllyl-6-nonenamide) is an acrid, volatile alkaloid responsible for hotness in peppers. While it is used as an ingredient in pepper sprays, capsaicin and its dihydro derivatives all exhibit antiinflammatory properties (Sancho et al., 2002). Kim et al. (2003) examined the anti-inflammatory mechanism of capsaicin on the production of inflammatory molecules in liposaccharides (LPS)-stimulated murine peritoneal macrophages. Capsaicin suppressed PGE2 production by inhibiting COX-2 enzyme and inducible nitric-oxide synthase (iNOS) expression in a dose-dependent manner. The inflammatory action of capsaicin was independent of the vanilloid-receptor 1 (VR-1) but involved the following signaling pathway (Scheme C.13). Capsazepine, a known VR-1 antagonist, did not eliminate capsaicin action, but inhibited COX-2 and iNOS expression.

Both compounds inactivated NF- κ B via stabilization of I κ B- α protein and may be useful in ameliorating inflammatory diseases and cancer.

Capsaicin is also used as a topical cream for treating various neuropathic conditions. Richeux and coworkers (1999) cautioned against the misuse of preparations containing 0.075 percent of capsaicin, which could lead to DNA-strand lesions, with detrimental effects to cellular functions, resulting in cell death or mutagenesis. The chemoprotective effects of topical application of capsaicin on the dorsal skin of female ICR mice was attributed by Han et al. (2001) to its suppression of phorbol ester-induced activation of NF- κ B and activator protein-1 (AP-1) transcription factors. Lee et al.



Capsaicin. (Adapted from Zhou et al., *Life Sci.*, 74:935–968, 2004.)



SCHEME C.13 Proposed intracellular signaling pathways for the anti-inflammatory action of capsaicin or capsazepine in peritoneal macrophages, TRAP, tumor necrosis factor; CAP capsaicin; CZE Capsazepine. (From Kim et al., *Cell. Sig.*, 15:299–306, 2003. With permission.)

(2000) showed capsaicin induced apoptosis in A172 human glioblastoma cells in a time- and dose-dependent manner. The mechanism whereby capsaicin induced apoptosis may involve reduction of the basal generation of ROS. Capsaicin's ability to induce apoptosis in SK-Hep-1 hepatocarcinoma cells was shown by Jung and coworkers (2001) to be due to its ability to reduce the ratio of antiapoptotic Bcl-2 to proapoptotic Bax and by activation of caspase-3.

While an early Italian case-control study showed chili consumption protected against stomach cancer (Buiatti et al., 1989), a subsequent epidemiologic study in Mexico City found a greater risk of developing stomach cancer (Lopez-Carrillo et al., 1994). Based on a number of studies, capsaicin appeared to both promote and inhibit chemically induced carcinogenesis. Further work is needed to confirm its chemopreventive properties.

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Capsicum

see Paprika

Caraway

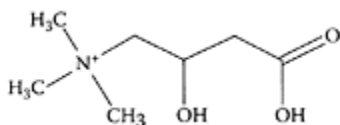
A reference-controlled doubleblind equivalence study by Madisch et al. (1999) showed a mixture of caraway and peppermint oil was comparable to the prokinetic agent cisapride in the treatment of functional dyspepsia. Further research by Freise and Kohler (1999) on nonulcer dyspepsia confirmed that an enteric-coated capsule containing peppermint and caraway oil was comparable in efficacy to that of an enteric-soluble formulation composed of peppermint and caraway oil. Micklefield and coworkers (2000) subsequently demonstrated the safe application of entericcoated and nonenteric-coated peppermint-caraway oil combinations for the treatment of gastroduodenal motility.

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L-Carnitine

L-Carnitine (β -hydroxy- γ -tri-methylammonium butyric acid), a small, water-soluble compound, is synthesized endogenously in humans, but most comes from the diet. The majority of L-carnitine on the market is produced by chemical synthesis. L-Carnitine plays an important role in mammalian fat metabolism as a fatty-acid carrier across the inner mitochondrial membrane, which undergoes β -oxidation for energy production. It has a number of important clinical applications,



L-Carnitine. (From Ilias et al., *Mitochondrion*, 4:163–168, 2004. With permission.)

including the treatment of heart disease, hemodialysis, and Alzheimer’s disease (Cederbaum et al., 1984; Brenningstall, 1990; Seim et al., 2001). Dayanandan and coworkers (2001) showed L-carnitine protected atherosclerotic rats by significantly reducing lipid-peroxidation levels in their hearts, as well as restoring the levels of enzymatic oxidants, superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and glucose 6 phosphate dehydrogenase (G6PD), and antioxidant vitamins C, E, and B₆ (Table C.17). A similar pattern was observed for the antioxidants and lipid peroxidation in the liver from the same atherosclerotic rats. By restoring the levels of these antioxidants, carnitine ensured that normal cell function was maintained.

Doxorubicin (DOX), an anthracycline antibiotic, is effective in reducing soft and solid tumors. However, its clinical application is somewhat limited by its severe cardiotoxicity due to the generation of cytotoxic aldehydes (Luo et al., 1999). These same researchers showed it was possible to attenuate the production of these peroxidation products by DOX by administering L-carnitine. The protective effect of L-carnitine was attributed to improving cardiac-energy metabolism and reduction in lipid peroxidation.

Male infertility is a serious problem in Western countries due, in part, to a decline in semen quality. The drugs used by practitioners and specialists for improving sperm quality have never really been tested. Lenzi et al. (1993) examined the effect of antioxidant therapies on sperm maturation. Both free and acetylated forms of L-carnitine are used by the spermatozoa for β -oxidation and for the transfer of acyl to mitochondrial CoA (Frenkel and McGarry, 1980; Peluso et al., 2000). Lenzi and coworkers (2003) treated 100 infertile patients (20–40 years) in a placebo-controlled, double-blind, crossover study with 2 g/day L-carnitine or the

TABLE C.17

Lipid Peroxidation and Antioxidant Levels in the Heart of Normal and Atherosclerotic Rats¹

	Normal Rats Treated with Saline	Atherosclerotic Rats Treated with	
		Saline	Carinitine (14 days)
Lipid peroxidation (nmoles MDA released/mg protein)	1.8+0.12	2.3+0.21*	1.9+0.14**
SOD (units/min/mg/protein)	8.4+0.71	5.3+0.58*	6.7+0.63**
CATALASE (umoles of GSH)	49.1+3.61	37.3+3.10*	45.7+3.70**

utilized/min/mg protein)			
GPx (μmoles of GSH utilized/min/mg protein)	5.8±0.48	4.1±0.32*	5.4±0.45**
G6PD (μmg/mg protein)	1.8±0.18	1.5±0.14*	1.8±0.17**
Vitamin C (μmg/mg protein)	2.1±0.13	1.4±0.14*	1.9±0.18**
Vitamin E (μmg/mg protein)	1.3±0.16	1.0±0.09*	1.2±0.09**
Vitamin B ₆ (μmg/mg protein)	133.6±12.0	93.7±11.0*	120.2±13.3**

¹Values expressed as mean±SD for six animals in each group.

²Amount of enzyme to inhibit autoxidation of pyrogallol by 50 percent in a standard 3 mL assay. For statistical evaluation, saline-treated atherosclerotic rats were compared with saline-treated normal **p*<0.05 and on comparing saline-treated atherosclerotic rats with carnitine treated atherosclerotic rats ***p*<0.01, ****p*<0.001.

Source: Adapted from Dayanandan et al., *J. Nutr. Biochem.*, 12:254–257, 2001.

placebo over two two-month periods. L-Carnitine therapy significantly improved semen quality, as measured by sperm concentration and total and forward motility. The potential of L-carnitine as a treatment for male infertility needs to be repeated using a much larger clinical trial and *in vitro* studies.

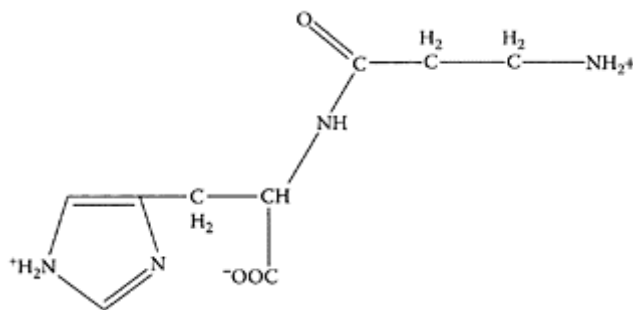
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L-Carnosine

L-Carnosine (β -alanyl-L-histidine) and its related compounds, anserine and homocarnosine, are found in the skeletal muscle and brain of mammals (Kohen et al., 1988). In addition to their antioxidant properties, they are efficient, copper-chelating agents with a possible role in copper metabolism (Gercken et al., 1980). Choi and coworkers (1999) showed carnosine-related compounds protected Cu,



L-Carnosine. (From Hobart et al., *Life Sci.*, 75:1379–1389, 2004. With permission.)

Zn-SOD (superoxide dismutase) from fragmentation by hydrogen peroxide. Carnosine and related compounds were shown by Ukeda and coworkers (2002) to protect human Cu, Zn-SOD from inactivation by glycoaldehyde, a Maillard-reaction intermediate, and from fructose. This protection was attributed to its hydroxyl radical-scavenging activity. Kang and coworkers (2002) showed L-carnosine's antioxidant properties protected rat liver epithelial cells from 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA) or hydrogen peroxide-induced apoptosis via the mitochondria.

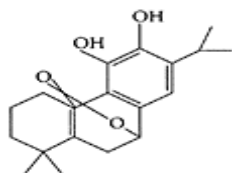
Carnosine, a histidine dipeptide in mammalian brain, has been shown to prevent neuronal toxicity (Hipkiss et al., 1997), ischemic injury (Stvolinsky et al., 1999), thermal injury (Deev et al., 1997), and β -amyloid aggregation (Munch et al., 1997). The anticross-linking property of carnosine appeared to be responsible for its potential use in the treatment of Alzheimer's disease (Hobart et al., 2004). The imidazolium group of histidine in carnosine may stabilize adducts formed with the primary amino group.

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Carnosol

see also Rosemary Carnosol is a phenolic dieterpene antioxidant obtained from the herb rosemary (*Rosemarinus officinalis Labiatae*). Its anticancer properties were demonstrated in animal models for breast and skin



Carnosol. (From Huang et al., *Biochem. Pharmacol.*, 69:221–232, 2005. With permission.)

tumors (Huang et al., 1994; Singletary et al., 1996). Carnosol was shown to strongly inhibit the activity of phase I enzyme, CYP 450, while stimulating the activities of phase II enzymes, glutathione S-transferase (GST), and NAD (P)H-quinone reductase (QR) in the liver (Offord et al., 1998). Dorrie and coworkers (2001) showed carnosol was effective against several pro-B and pre-B acute lymphoblastic leukemia (ALL) lines, a disease prevalent among infants during early childhood. Carnosol induced apoptosis in B-lineage leukemias by down-regulating the antiapoptotic protein Bcl2, suggesting it was a novel chemotherapeutic agent against other types of cancers. It proved cytotoxic against all five acute leukemia lines, with the percentage of dead cells ranging from 40 to 75 percent with the effect of 6 $\mu\text{g/mL}$ of carnosol not statistically different from that of 9 $\mu\text{g/mL}$ (Figure C.20). A recent study by Huang et al. (2005) showed the potential of carnosol for treating lung metastasis of B16/F10 mouse melanoma cells by inhibiting NF-6B and AP-1 binding activity. Following this, carnosol inhibited metalloproteinase (MMP)-9 gene expression which is associated with increased metastatic potential for many types of cancers.

The antioxidant properties of carnosol were demonstrated by Lo and coworkers (2002) by its ability to scavenge DPPH free radicals and protect DNA from the Fenton reaction.

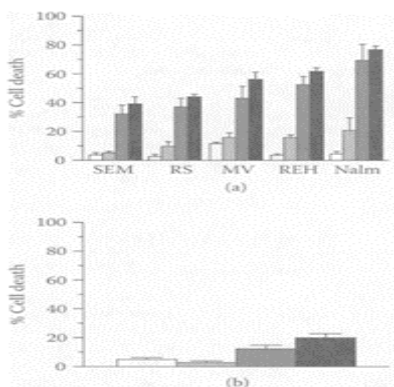


FIGURE C.20 Carnosol is cytotoxic to the leukemia cells (a). The leukemia cells lines; or (B), Peripheral blood mononuclear cells (PMBCs) from

healthy volunteers were untreated, or treated with 3 (gray), 6 (hatched), and 9 $\mu\text{g/mL}$ (black) carnosol, and the percentage cell death was measured after four days by propidium iodide staining of nuclei and a FACS-Calibur fluorescence-activated cell scorer (FACS). The data presented represent the mean of the percentage cell death \pm SE of five separate experiments for (A) and three healthy donors for (b). The control is white. (From Dorrie et al., *Cancer Lett.*, 170:33–39, 2001. With permission.)

Carnosol markedly reduced lipopolysaccharide (LPS)-stimulated NO production in mouse macrophages in a concentration-dependent manner, with an IC_{50} of 9.4 μM , while only slight changes were observed for the other rosemary compounds (carnosic, rosmarinic, and ursolic acids). Multiple stages of carcinogenesis and inflammation are characterized by large amounts of NO produced by inducible NO synthase (iNOS). The mechanism for carnosol's anticancer and anti-inflammatory properties appears to be related to its suppression of NO production and iNOS gene expression through inhibition of nuclear factor- κB (NF- κB).

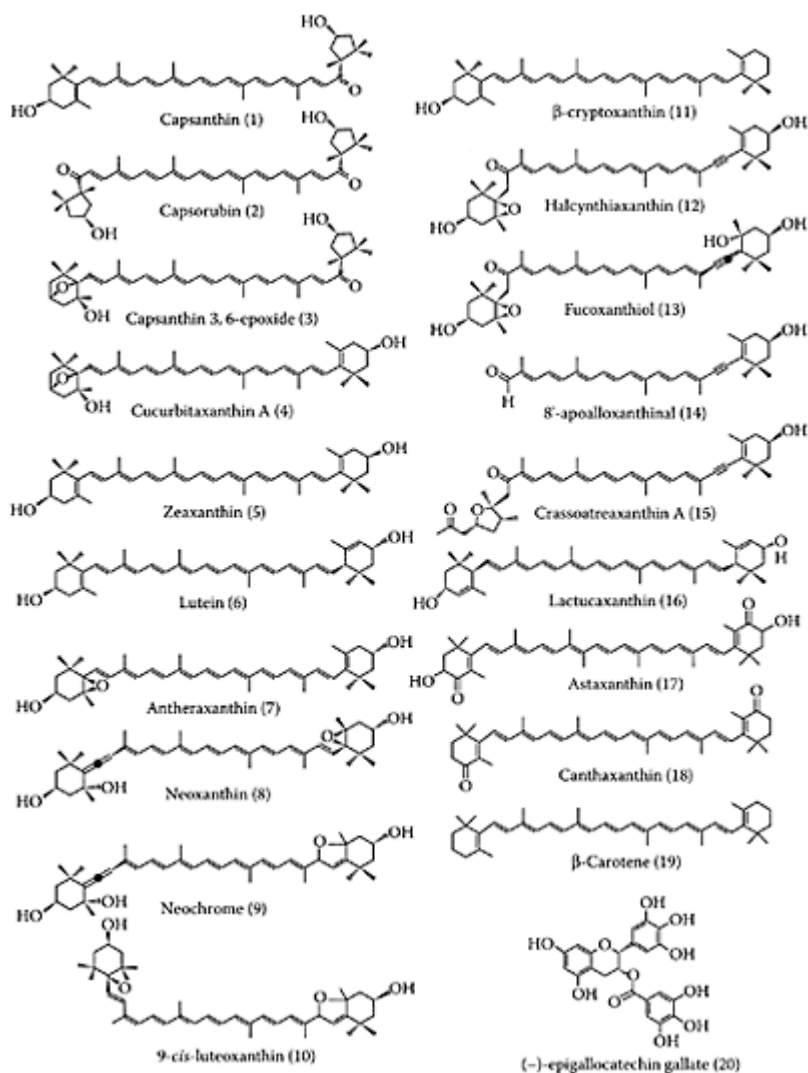
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Carotenoids

Consumption of diets high in fruits and vegetables has been associated with a decrease in cancer and cardiovascular diseases and possibly other degenerative diseases (Block et al., 1992; Willett, 1994; Ames et al., 1995). Of the 600 dietary carotenoids identified in fruits, vegetables, and fish, many of them are reported to protect against atherosclerosis, cancer, and macular degeneration, as well as act as photoprotectants against sun damage to the skin (Mares-Perlman et al., 1995; D'Odorico et al., 2000; Nishino et al., 2000; Ziegler and Vogt, 2002). As antioxidants, they scavenge free radicals or quench singlet oxygen. The association between oxygen radicals, such as superoxide ($\cdot\text{O}_2^-$) and nitric oxide (NO), and chronic diseases, such as cancer, makes carotenoids potentially important antioxidants in human health. However, a recent ATBC Study suggested that β -carotene, under certain circumstances, may enhance carcinogenesis (Rautalahtu et al., 1997). In addition to β -carotene, Murakami and coworkers (2000) examined the ability of 18 natural carotenoids to inhibit tumor-promoting 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced $\cdot\text{O}_2^-$ generation in differentiated human promyelocytic cell HL-60 cells (Scheme C.14). No cytotoxicity was observed for any of the carotenoids at 25 μM with inhibitory rates (IRs) ranging from -3.4 percent (for β -cryptoxanthin) to 52.6 percent (for halocynthiaxanthin). The 11 carotenoids all had superior or similar inhibitory rates (IRs=25.1–52.6 percent) to β -carotene (21.3 percent) and the green tea polyphenol, (-) epigallocatechin gallate (IR=15.6 percent). Murakami et al. (2000) proposed that carotenoids in fruits and vegetables suppressed leukocyte-induced oxidative stress by attenuating $\cdot\text{O}_2^-$ production systems, such as NADPH oxidase. From a structural point of view, the presence of a single, 3-hydroxy- κ -end group in carotenoids appeared important for this activity. For example, capsanthin 3,6-epoxide, with 3hydroxy- κ -end group, had a significantly higher inhibitory rate of 40.9 percent compared to 28.4 percent for cucurbitaxanthin, with a 3-hydroxy- β -end group. The ability of these same carotenoids to inhibit lipopolysaccharide (LPS) and interferon ($\text{IFN-}\gamma$)-induced NO generation by mouse macrophage RAW 264.7 cells ranged from -45.2 percent to +94.7 percent with no cytotoxicity reported for any of carotenoids at 50 μM . Halocynthiaxanthin from the Sastumas mandarin (*Citrus unshui*) exhibited the greatest inhibitory activity of 94.7 percent, indicating the importance of the 3-hydroxy- κ -end group for inhibiting NO production.

Kozuki and coworkers (2000) suggested the antioxidant properties of carotenoids, α -carotene, β -carotene, lycopene, β -cryptoxanthin, zeaxanthin, lutein, canthaxanthin, and astaxanthin, were responsible for inhibiting invasion of rat ascites hepatoma AH 109A cells in a dosedependent manner up to 5 μM . Using a model membrane environment composed of unilamellar dipalmitoyl phosphatidylcholine, Cantrell and coworkers (2003) found singlet oxygen quenching varied with the particular carotenoid incorporated. Lycopene and β -carotene had the



SCHEME C.14 Structure of carotenoids (1–19) and ECGC (20).
(From Murakami et al, *Cancer Lett.*, 149:115–123, 2000. With permission.)

fastest singlet oxygen-quenching rate, while lutein the least, with astaxanthin and canthaxanthin intermediate.

Considerable variability between the efficacy of different carotenoids was also shown by Pool-Zobel and coworkers (1997). These researchers showed that carotenoid-rich plant products, such as tomato juice, carrot juice, and spinach powder, consumed by 23

healthy, nonsmoking males between the ages of 27–40, all exerted cancer-protective effects. Using the Comet assay for DNA damage, which specifically measures oxidation of pyrimidines in DNA, only carrot juice reduced endogenous oxidative damage (Figure C.21).

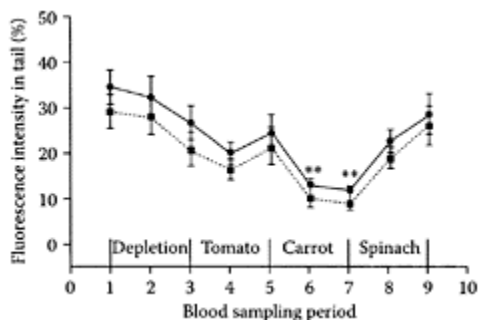


FIGURE C.21 Levels of DNA-strand breaks in peripheral blood lymphocytes from humans receiving different vegetable products. The extent of DNA damage is indicated by the percentage of fluorescence in the comet tail (“tail intensity”). Results are shown as means±SEM, n=21–23 subjects, means of three slides per subject.

*Statistically significant in comparison to sampling time 1; two-sided Student’s t-test, $p < 0.05$. (From Pool-Zobel et al., *Carcinogenesis*, 18:1847–1850, 1997. With permission.)

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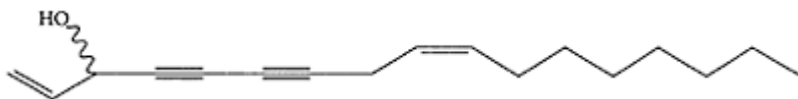
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Carrot

Carrot (*Daucus carota* L.), a biennial of the *Umbelliferae* family, is grown throughout the world. It is an excellent source of carotenoids, particularly β -carotene. Pool-Zobel et al. (1997) conducted a human-intervention study in which he fed healthy, young men 330 mL carrot juice, tomato juice, and dried-spinach powder. The carrot juice, containing 22.3 mg β -carotene and 15.7 mg α -carotene, was the only one to decrease base oxidation, an indicator of oxidative damage, which was attributed to the ability of α -carotene and β -carotene to quench free radicals *in vivo*.

However, in spite of carrots being high in β -carotene, there are conflicting data with respect to their health benefits. For example, supplementing well-nourished populations with β -carotene did not prevent cancers or other health disorders (The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994; Greenberg et al., 1996; Hennekens et al., 1996). In other cases, the incidence of cancer actually increased in smokers taking β -carotene supplements



Falcarinol. (From Brandt et al., *Trends Food Sci. Technol.*, 15:384–393, 2004. With permission.)

(Omenn et al., 1996). The beneficial health effects associated with the consumption of β -carotene-rich vegetables seems contradictory and, in the case of carrots, may be due to the presence of other bioactive compounds. Such compounds may be poly acetylenes, falcarinol, and falcarindiol, found in vegetables such as carrots. Falcarinol or panaxynol, (9Z)-hepta-deca-1,9-dien-4,6-diyn-3-ol, is reported to be one the most bioactive components in carrots (Brandt and Christensen, 2000). While it has been shown to be cytotoxic against several human tumor cells (Saita et al., 1993; Bernart et al., 1996), falcarinol is also a potent skin sensitizer and irritant, as well as a neurotoxic at high concentrations (Hansen and Boll, 1986; Hansen et al., 1986). Recent work by Hansen and coworkers (2003) found falcarinol had biphasic activity, stimulating human cancer growth and cell proliferation between 0.01–0.05 $\mu\text{g/mL}$, while inhibiting cell proliferation at concentrations greater than 1 $\mu\text{g/mL}$. Thus, the effect of falcarinol on cell proliferation was concentration-dependent. In comparison, β -carotene had no effect as either a stimulator or inhibitor. Long-term storage, however, resulted in a 35 percent loss of falcarinol, while carrot pieces boiled in water suffered a 70 percent loss (Figure C.22). To maximize the health benefits derived from carrots, eating them raw was recommended.

Stoll et al. (2003) developed a pilot-plant scale process for recovering carotenoids from carrot pomace. The total carotene content (α - and β -carotene) of the concentrated hydroly sate was 64 g/kg, making it an excellent functional-food ingredient. Chau and coworkers (2004) showed carrot pomace was rich in insoluble fibers composed mainly of pectin material, hemicellulose, and cellulose. In particular, the water-insoluble solids exhibited significantly ($p < 0.05$) greater glucose absorption and amylase-inhibitory activities compared to cellulose. The hypoglycemic effects of some of these fractions could be useful in controlling postprandial glucose levels.

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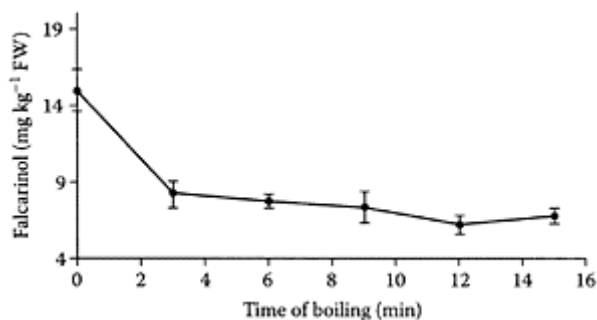


FIGURE C.22 Reduction in falcarinol content in carrot pieces during boiling in water. Values are mean \pm SD of three processing replications. FW=fresh weight. (From Hansen et al., *J. Sci. Food Agric.*, 83:1010–1017, 2003.)

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Casein

Casein is an important nutritional source of milk protein. Early studies showed that casein inhibited lipid oxidation by molecular encapsulation of the 1,4-pentadiene fatty acids (Laakso, 1984). To determine the primary sequence in casein responsible for its free-radical-scavenging activity, Suetsuna and coworkers (2000) examined peptides produced by peptic digestion of casein. A number of peptides exhibiting superoxide anion-scavenging activity (SOSA) were isolated in which the amino-acid sequence was Tyr-Phe-Tyr-Pro-Glu-leu (YFYPEL). Of the amino acids in the peptide, Glu-Leu appeared important for activity. Casein protein was also recognized as an important source of biologically active peptides (Chabance et al., 1998). Such peptides play an important role in the development of the immune system in newborns. Immunostimulating peptides identified in bovine casein were LLY (residues 191–193 β -casein), TTMLPW (C-terminal hexapeptide of α_{s1} -casein), and PGPIP (residues 63–68 of β -casein) (Fiat et al., 1993). Xiao and coworkers (2000) investigated the effect of these three peptides on the production of tumor necrosis factor- α (TNF- α) and interleukine-6 (IL-6). The latter are multifunctional cytokines released by macrophages and play an important role in immunoregulation and host defenses (Akira et al., 1990). Xiao et al. (2000) also found that incubation of these three bovine-casein peptides with murine bonemarrow macrophages in the presence of lipopolysaccharide enhanced TNF- α and IL-6 production and nitric-oxide release. These changes could be important in the defense by the host against infection by pathogens.

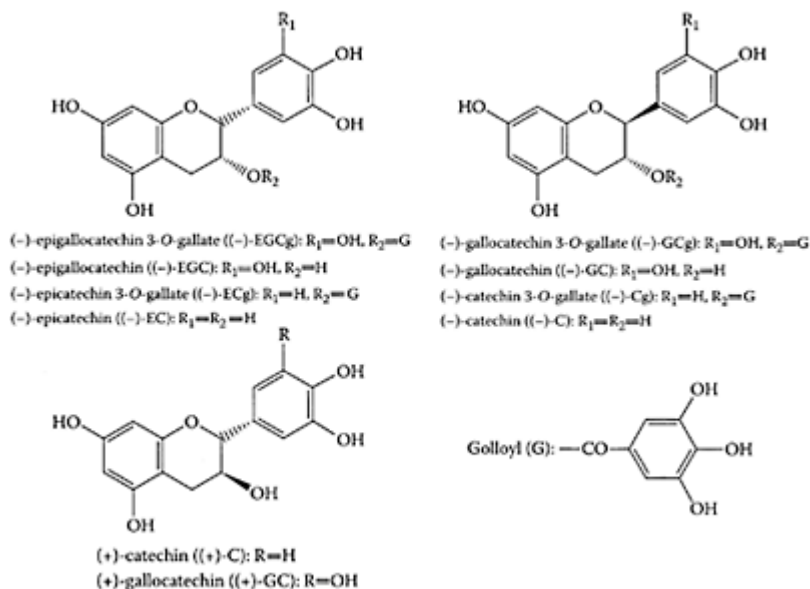
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Catechins

Catechins are polyphenols widely distributed in fruits and vegetables, especially in tea (Scheme C.15). They have been shown to be anticarcinogenic, antiatherosclerotic, antimicrobial, and to act as antioxidants (Wang et al., 2000; Yang et al, 2000; Yang et al, 2001; McKay and Blumberg, 2002). In addition to scavenging free radicals, tea catechins may also modulate some cellular enzymes. Blache et al. (2002) studied the effect of (+)-catechin on acute iron-load-induced model of platelet hyperactivity. Beneficial effects were only observed in the iron-loaded animals and attributed to antioxidant properties of catechin or its metabolites. The presence of galloyl and gallate moieties in tea catechins, such as (–)-epicatechin gallate (ECG) and (–)-epigallocatechin gallate (EGCG), appears to enhance the antibacterial, anticancer, and radical-scavenging properties of catechin (Ikigai et al., 1993; Rice-Evans, 1995; Kitano et al., 1997). Caturla and coworkers (2003) examined the interaction of



SCHEME C.15 Tea catechin structures. (From Nishitani and

four catechins from green tea and vegetables, (+)-catechin (C), (–)-epicatechin (EC), (–)-epicatechin gallate (ECG), and (–)-epi-gallocatechin gallate (EGCG), with phospholipid-model membranes composed of 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) or 1,2-dielaidoyl-sn-glycero-3-phosphoethanolamine (DEPE). Galloylated catechins, particularly ECG, affected the physical properties of phospholipid membranes by increasing lipid order and promoting the formation of detergent-resistant structures deep inside. In comparison, the nongalloylated catechins were located close to the phospholipid/water interface. ECG exhibited the highest antioxidant activity in this system, while EGCG produced leakage from *E. coli*-isolated membranes via a specific interaction with phosphatidylethanolamine. The effects on the membranes by galloylated catechins could explain their multiple biological activities.

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Cat's claw (*Uncaria tomentosa*)

see also Quinic acid Cat's claw, a vine grown in Peru, has been used as a traditional medicine for treating a wide range of ailments, particularly digestive problems and arthritis. An *in vitro* oxidant-induced stress study by Sandoval and coworkers (1998) showed Cat's claw acted as an antiinflammatory agent by protecting the cells from oxidative stress, as well as inhibiting activation of NF- κ B. Of the two species examined, *U. guianensis*, with much lower levels of oxindole or pentacyclic alkaloids, was far more potent. This suggested the latter compounds did not contribute to Cat's claw's antioxidant and antiinflammatory properties. Further work by Sandoval et al. (2000) examined the effect of Cat's claw on other NF- κ B-regulated genes implicated in inflammation as other examples of oxidative injury. Freeze-dried and micropulverized aqueous extracts from Cat's claw both inhibited DPPH in a dose-dependent manner. Of the two extracts, the freeze-dried one was far more effective (Figure C.23). In addition, there was a significant reduction in TNF- α , an NF- κ B-dependent cytokine involved in chronic inflammation. The freeze-dried extract again proved to be the more potent inhibitor of TNF- α and was 1.5×10^4 more effective than its antioxidant activity. Ganzera et al. (2001) reported the alkaloid content of different samples of Cat's claw and its market products ranged from 0.156–0.962 percent. Angular and coworkers (2002) showed a spray-dried hydroalcoholic extract from Cat's claw had a significantly higher ($p < 0.05$) anti-inflammatory activity compared to an aqueous freeze-dried extract using the carrageenan-induced paw oedema model. The presence of pentacyclic oxindole alkaloids acting alone or synergistically with other metabolites were effective at concentrations as low as 0.001 $\mu\text{g/mL}$. Recent research,

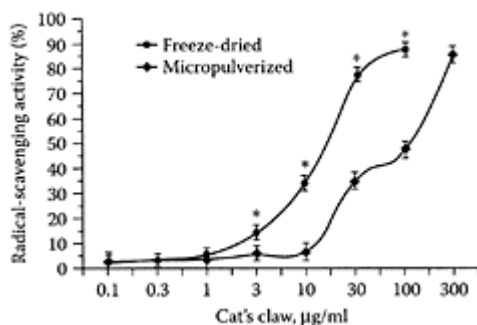


FIGURE C.23 Antioxidant activity of micropulverized and freeze-dried aqueous Cat's claw extracts, assessed by the DPPH radical method. Values are mean \pm SEM of three experiments with three samples each. *Significant

inhibition ($p<0.001$) compared to same concentration of micropulverized Cat's claw. (From Sandoval et al., *Free Rad. Biol. Med.*, 29:1–78, 2000. With permission.)

however, points to quinic-acid esters as active ingredients in Cat's claw water extracts (Sheng et al., 2005).

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Cauliflower

see S-methylmethane thio-sulfonate

Cereal grains

see also Barley, Oats, Wheat, and Rice Cereal grains contribute approximately 30 percent of the total dietary energy intake in adults in Britain and many other Western countries. Truswell (2002) reviewed the possible relationship between cereal-grain consumption and coronary heart disease (CHD). For example, in the scientific literature, oat fiber was far more effective in lowering total and LDL cholesterol compared to wheat

fiber. Rice bran also lowers cholesterol. Based on his review, the author validates the health claim that whole-grain cereal foods and oat meal or bran lower cholesterol and the risk for CHD.

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Chamomile

Chamomile, a perennial flowering plant, grows well in the wild in Europe, particularly Croatia and Hungary. Many plants are called chamomile or have it as part of their common name. Five species in the United Kingdom and Europe include German chamomile (*Matricaria recucita*), Roman chamomile (*Chamaemelum nobile* or *Anthenis nobile*), foetid or stinking weed (*A. Cotula*), corn chamomile (*A. Arvensis*), and yellow chamomile. Roman chamomile (*Chamaemelum nobile* or *Anthenis nobile*) is the one most often referred to in English herbals. Commercially grown as a double-flowered form and, like chamomile, has an aromatic bitterness, the chamomile plant (*Matricaria chamomilla*), a member of the *Asteracea* family, is used as a medicinal tea for treating fever, diarrhea, menstrual pain, and inflammation, as well as intestinal and hepatic disorders (Mann and Staba, 1986). It is also the active principle in creams for atopic eczema (Patzelt-Wenczler and Ponce-Poschl, 2000).

One of the major components in chamomile is the flavonoid apigenin (see Apigenin), which

TABLE C.18

Main Components in Chamomile Essential Oil	
Component	%
(E)- β-Farnesene	28.8
α-Bisabolol oxide A	41.8
α-Bisabolol oxide B	4.3
α-Bisabolol oxide	5.3
β-Bisabolol oxide	2.3
Germacrene-D	2.2
Chamazulene	2.2
(Z,E)- α-Farnesene	1.6

was found to inhibit adhesion-molecular expression, prostaglandin, and cyclooxygenase, as well as the proinflammatory cytokine interleukin (IL)-6 in cell culture (Panes et al., 1986). Smolinski and Pestka (2003) showed chamomile apigenin inhibited LPS-induced IL-6 and TNF- α production in cell culture, further confirming its anti-inflammatory properties.

The oil component in chamomile, comprising less than 2 percent, contains the terpene bisabolol, and the sesquiterpenes matricine and chamazulene, both of which exhibit antiinflammatory properties (Jakolev et al., 1983; Villegas et al., 2001). Hernandez-Ceruelos and coworkers (2002) identified 13 compounds in chamomile essential oil (Table C.18). α -Bisabolol oxide A and (*E*)- β -farnesene accounted for just under 70 percent of the total, while the remainder included smaller amounts of various bisabolol oxides, chamazulene and germacrene. These researchers clearly demonstrated the effectiveness of chamomile essential oil to inhibit sister chromatid exchanges induced by mutagens, daunorubicin and methyl methanesulfonate, in mouse bone-marrow cells. The antineoplastic daunorubicin acts on DNA through the production of free radicals, causing genotoxic damage, such as an increase in the rate of sister chromatid exchanges (Noviello et al., 1994). The results for daunorubicin, summarized in Table C.19, show Chamomile (CO) significantly reduced genotoxic damage in a dose-dependent manner. Addition of 5, 50, and 500 mg/kg of CO, in the presence of 10 mg/kg of dauorubicin, resulted in an antigenotoxic response corresponding to 25.8 percent, 63.1 percent, and 75.6 percent, respectively. A similar effect was observed for methyl methanesulf onate (MMS), in which the corresponding antigenotic responses for 250, 500, and 1000 mg/kg of CO, in the presence of 25 mg/kg MMS, were 24.8 percent, 45.8 percent, and 60.6 percent, respectively. While consumption of green tea was reported to reduce human oxidative stress, the ability of chamomile tea to act in a similar manner requires further investigation.

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TABLE C.19

Effect of Chamomile Oil (CO) on Sister Chromatide Exchanges (SCEs) Induced by Dauorubicin (Dau) in Mouse Bone-Marrow Cells

	Dose (mg/kg)	Mice No.	SCE ¹ X+E.D.	Inhibition (%)
Corn oil	0	5	1.57+0.31*	
CO	500	5	1.53+0.30*	
Dau	10	5	11.0+1.49	
CO+Dau	5+10	5	8.59+1.20*	25.79
CO+Dau	50+10	5	5.06+0.59*	63.1
CO+Dau	500+10	5	3.88+0.65*	75.58

¹Each SCE value is the mean of 30 second-division cells per mouse. *Statistically significant difference with respect to the value of Dau.

Source: Adapted from Hernandez-Ceruelos et al., *Toxicol. Lett.*, 135:103–110, 2002.

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Chasteberry

The dried ripe fruit from the Chasteberry tree (*Vitex*) has been used to treat female reproductive problems since ancient Greece (Brown, 1994). It was also used to decrease sexual desire in men during medieval times, hence, the name chaste tree or monk’s pepper (Snow, 1996). In Germany, it is a well-recognized treatment for menstrual irregularities and premenstrual syndrome (PMS) (Blumenthal et al., 1998). Extracts of chasteberry tree berries were shown to bind dopamine receptors in the anterior pituitary, decreasing the basal- and thyrotropin-release-hormone that secretes prolactin (Jarry et al., 1994; Sliutz et al., 1993). In the second and third week of their cycles, women suffering from PMS have markedly higher levels of prolactin (Halbreich, 1976). The successful

treatment of PMS by *Vitex* was attributed to its ability to reduce prolactin (Bohnert, 1997; Mayo, 1997). The active ingredients in chasteberry are iridoid glycosides-agnuside (0.6 percent) and aucubin (0.3 percent), together with flavonoids and essential oils (Gomaa et al., 1978). Dittmar and coworkers (1992) treated 175 women suffering from PMS with *Vitex* or pyridoxine and evaluated them during the second half of their menstrual cycle with a Premenstrual Tension Scale and the CGI scale. The efficacy of the CGI score for *Vitex* was 77.1 percent compared to 60.6 percent for pyridoxine. While no drug interactions have been reported for *Vitex*, it could counteract the effectiveness of birth-control pills because of its effect on prolactin (Feldmann et al., 1990).

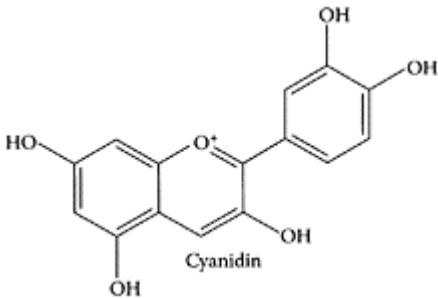
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Cherries

Cherries are highly colored fruit rich in anthocyanins. For example, Wang and coworkers (1999a) showed that anthocyanins and cyanidin isolated from tart cherries had antioxidant and anti-inflammatory properties similar to commercial products. These researchers (Wang et al., 1999b) identified, in addition to chlorogenic acid methyl ester, three novel antioxidants in tart cherries, such as 2hydroxy-3-(*o*-hydroxyphenyl) propanoic acid, 1-(3',4'-dihydroxycinnamoyl)-cyclopenta-2,5-diol, and 1-(3',4'-dihydroxycinnamoyl)-cyclo-penta-2,3-diol. Tart-cherry anthocyanin extracts were shown by Tall et al. (2004) to be beneficial for treating inflammatory pain. Using an acute-inflammation rat model, an equivalent reduction in inflammation-induced thermal hyper

algesia, mechanical hyperalgesia, and paw edema was evident with the highest dose of tartcherry extract (400 mg/kg) compared to the drug indomethacin (5 mg/kg). The potential of tart-cherry anthocyanins to reduce persistent and chronic pain in patients is promising, but requires further clinical studies.



(Adapted from Kang et al., *Cancer Lett.*, 194:13–19, 2003.)

Kang et al. (2003) showed tart-cherry anthocyanins and the aglycone cyanidin all inhibited the development of intestinal tumors in Apc^{Min} mice, as well as the growth of colonic tumors in human colon-cancer cell lines HT29 and HCT 116. Cyanidin was far more effective than anthocyanins in inhibiting the growth of these human colon-cancer cells, as shown in Figure C.24.

This was evident by the IC₅₀ values for cyanidin being 85 and 63 μM for the HCT 116 and HT 29 cells compared to 260 and 585 μM for the anthocyanins.

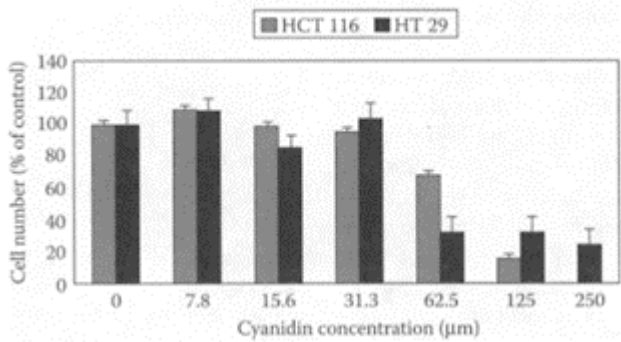


FIGURE C.24 Effect of cyanidin on the growth of human colon-cancer cells. Gray bars, HCT 116 cells; black bars, HT 29 cells. Error bars=Standard error of the mean. (From Kang et al., *Cancer Lett.*, 194:13–19, 2003. With permission.)

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Chickpea

Chickpea (*Cicer arietinum* L.) is the third most important grain legume based on total production (FAO, 1994). It is a rich source of dietary protein because of its well-balanced amino-acid composition, bioavailability, and low levels of antinutritional factors compared to other legumes (Friedman, 1996). The importance of legumes such as chickpeas is related to it being one of the low-glycemic index (GI) foods. The importance of such foods is due to their ability to improve metabolic control of hyperlipidemia in diabetic and healthy individuals (Frost et al., 1999; Jenkins et al., 1994). The classification of GI is based on the postprandial blood-glucose response based on the rate of digestion and absorption of carbohydrates present in the food. Goni and ValentinGamazo (2003) prepared three test meals of 50 g carbohydrates, including a spaghetti, in which wheat was partially replaced with chickpea flour (25 percent), a wheat spaghetti, and white bread. While the two spaghettis had similar levels of resistant starch and dietary fiber, the indigestible fraction was significantly higher in the chickpea-containing product. When fed to 12 healthy volunteers, the postprandial rise in blood glucose was much smaller with the chickpea product with a GI of 58±6 compared to 73±5 for the corresponding 100 percent wheat

TABLE C.20

Inhibition of ACE by Peptidic Fractions Obtained by Reverse-Phase Chromatography of a Chickpea Legumin Hydrolysate. Effluent from C₁₈ HPLC Were Pooled in Six Fractions and Analyzed for ACE-Inhibitory Activity

Fractions	Inhibition of ACE
(Elution Time, Min)	(% Residual Activity)
0–10	97
10–15	90

15–20	92
20–25	78
25–30	76
35–40	58

Source: From Yust et al., *Food Chem.*, 81:363–369, 2003. With permission.

pasta. The low glycemic response observed for the product containing chickpea could lead to its incorporation to produce other low-GI foods.

The main storage protein of chickpea is legumin, a globulin composed of six $\alpha\beta$ subunits. Yust et al. (2003) examined the production of bioactive peptides by subjecting chickpea legumin to expensive and nonspecific protease. Of the min to proteolytic digestion with alcalase, an peptidic fractions isolated by reverse-phase chromatography, only those with the longest retention times (35–45 min) had high ACE-inhibitory activity (Table C.20). This is not unexpected, as ACE-inhibitory activity peptides usually contain hydrophobic amino acids, which interact more with the column, taking a longer time to be eluted. Further examination of these peptides confirmed the presence of hydrophobic amino acids, with methionine detected as the most abundant. Identification of chickpea peptides with ACE-inhibitory activity suggests their possible use in lowering blood pressure *in vivo*.

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Chilean berry (*Aristotelia chilensis*)

Chilean berry (*ach*) is an edible, black-colored fruit with medicinal properties. *Ach* was found to contain six indole alkaloids (Kan et al., 1997). Recent studies by Miranda-Rottmann and coworkers (2002) showed *ach* was a much richer source of phenolic

antioxidants compared to cranberry, blueberry, blackberry, strawberry, raspberry, and red wine. In addition, *ach* also had the highest scores for total radicaltrapping potential and total antioxidant reactivity in *in vitro* antioxidant tests. Most of *ach*'s antioxidant properties were in the anthocyaninrich fraction of the juice. It was responsible for the effective inhibition of copper-induced LDL oxidation and the dose-response protection of hydrogen-peroxide-induced intracellular oxidative stress in human endothelial-cell cultures.

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Chili peppers

see also Capsaicin Chili peppers, a member of the *Capsicum* family, are consumed extensively as spices. The principal pungent and irritant ingredient in chili peppers is capsaicin. A discussion of the health-related properties of chili peppers can be found under capsaicin.

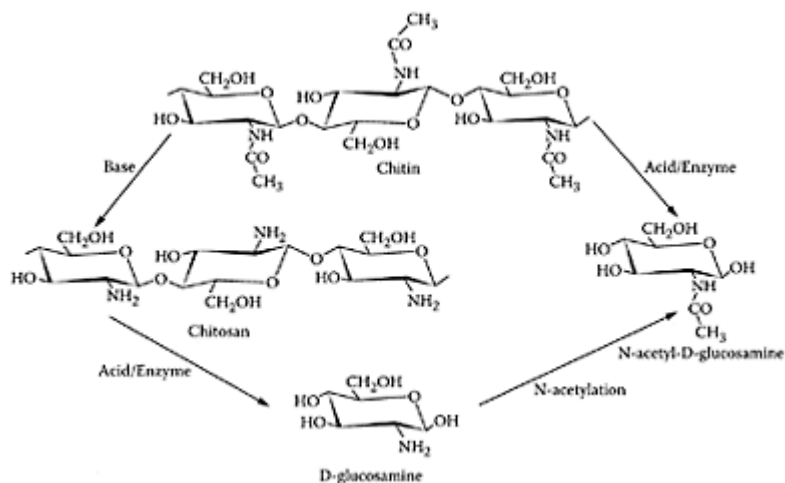
Chinese herbs

In China, the idea that food and medicine were equally important for preventing and curing diseases has been passed down to the present day from the ancient legend describing an herbalist, Shennong, who tasted many different types of herbs (Zhang, 1990). With the development of functional foods and nutraceuticals, attempts are being made to bridge the typical Chinese medicated diet and functional foods and nutraceuticals (Xu, 2001). Chinese herbal extracts have been used to treat a variety of cancers, but their efficacy on pancreatic cancer has not been reported. Schwartz and coworkers (2003) examined the effect of ethanol extracts of two quality-controlled, dried, encapsulated supplements of 15 (SPES) and eight (PC-SPES) Chinese herbs on eight human pancreatic-cancer-cell lines. Both extracts were significantly toxic to the pancreatic-cancer cells and induced apoptosis. Both extracts, however, need further evaluation as agents for the clinical treatment of pancreatic cancer. SPES could be combined with

cellcycle-independent cytotoxic drugs, while PCSPES, because of its G2-blocking pattern, may be useful as a radiation sensitizer.

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SCHEME C.1 6 Preparation of chitin derivatives. (From Shahidi et al., *Trends Food Sci. Technol.*, 10:97–105, 1999. With permission.)

Chitin and chitosan

Chitin is the next most abundant polysaccharide in nature after cellulose. It is a natural polymer composed of the aminosugar *N*-acetylglucosamine. The major deacetylated form of chitin, chitosan, is found in crustaceans, such as crabs, lobsters, and shrimp. It is a versatile biopolymer with many derivatives formed, as shown in Scheme C.16 (Shahidi et al., 1999). Since chitin and chitosan are both capable of complexing transition metals,

Kamil and coworkers (2002) examined its potential as an antioxidant. Using chitosans of different viscosity, these researchers found that lower-viscosity chitosan exhibited strong antioxidant activity and could be a potential source of natural antioxidant for stabilizing lipid-containing foods. Chitosan also appeared to enhance intestinal permeability, permitting the absorption of hydrophilic drugs (Kotze et al., 1997). Recent work by Ranaldi and coworkers (2002) suggested that chitosan ingestion altered intestinal-barrier function, permitting the entry of potentially toxic or allergenic substances. Taha and Swailam (2002) noted that 0.04 percent of chitosan suppressed the growth and hemolysin production of *Aeromonas hydrophilia*. Song and coworkers (2002) improved the solubility of chitosan by conjugating it with lysozyme via a Maillard-type reaction. The resulting chitosan-lysozyme conjugate had enhanced emulsifying properties and bactericidal action against *Escherichia coli* K-12.

Chitosan was also found to increase fat elimination in the stool of rats (Sugano et al., 1980; Ebihara and Schneeman, 1989). In addition, dietary chitosan reduced cholesterol in rats, suggesting it as a possible dietary supplement. Bokura and Kobayashi (2003) recently reported chitosan significantly reduced total cholesterol in female volunteers with mild to moderate hypercholesterolemia. In the subgroup, more than 60 years of age, there was a greater tendency for cholesterol reduction in the chitosan group compared to the placebo group (Table C.21). After eight weeks of treatment, total cholesterol in the chitosan group decreased from 241 to 226 mg/dL, while the placebo remained essentially the same. A significant reduction was also observed for LDL cholesterol in the chitosan group, while the placebo group remained unchanged.

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TABLE C.21

Values of Serum Lipids of Subjects with More Than 60 Y of Age^{1,2}

Parameter	Baseline		Eight-Week Assessment	
	Chitosan	Placebo	Chitosan	Placebo
Total cholesterol (mg/dL)	241+30	237+26	226+29*	242+27
HDL cholesterol (mg/dL)	66+18	67+12	64+15	66+12
LDL cholesterol (mg/dL)	153+28	152+27	135+22**	151+24
Triglycerides (mg/dL)	130+62	95+38	110+55	94+35

¹Chitosan, n=16; placebo, n=20

²**p*<0.05; ***p*<0.01 compared with the baseline,

Source: Adapted from Bokura and Kobayashi, *Eur. J. Clin. Nutr.*, 57:721–725, 2003.

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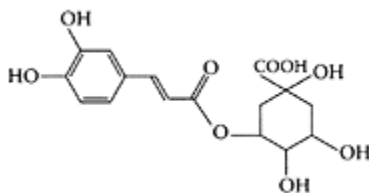
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Chlorogenic acid

Fruit and vegetable extracts, such as obtained from carrots, burdock (gobou), apricot, and prune, were found to inhibit the formation of 8-hydroxydeoxyguanosine (8-OH-dG) (Kasai et al., 2000). 8-OH-dG, a key marker of cellular oxidative stress during carcinogenesis, induces point mutations in mammalian cells (Kasai, 1997). A common inhibitor in these extracts was chlorogenic acid, which was shown to inhibit 8-OH-dG in a rat-tongue carcinogenesis model.



Chlorogenic acid. (From Wen et al., *Food Microbiol.*, 20:305–311, 2003. With permission.)

Chlorogenic acid (CGA), an esterified product of caffeic acid and quinic acid, was reported by Hemmerle and coworkers (1997) to modulate glucose-6-phosphatase, an enzyme involved in glucose metabolism. Nardini et al. (1995, 1997) also showed it decreased oxidation of LDL cholesterol and total cholesterol, thereby reducing the risk of cardiovascular disease. Rodrigues de Sotillo and Hadley (2002) found a significant

reduction in plasma triacylglycerols, total cholesterol, and postprandial glucose in Zucker rats treated with chlorogenic acid.

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Chlorophyll and chlorophyllin

see also Pheophytin and Pheophorbide Epidemiological studies associated consumption of dark-green vegetables, rich sources of chlorophyll pigments, with cancer protection. Antigenotoxic properties of chlorophylls were subsequently demonstrated using short-term genotoxicity assays (Dashwood, 1997; Negishi et al., 1997; Dashwood et al., 1998). Insolubility of chlorophyll in aqueous solutions, however, led to an investigation of the chemoprotective effects of its stable, water-soluble derivative, chlorophyllin (CHL). Porphyrin compounds, such as chlorophyll and CHL, were known to protect against a variety of direct- and indirect-acting mutagens, such as aflatoxin B1, heterocyclic amines, and nitrosamines (Dashwood et al., 1991; Guo et al., 1995; Romert et al., 1992; Hayatsu et al., 1999). Further studies confirmed the anticancer properties of CHL by its inhibition of induction of hepatocarcinogenesis by aflatoxin B1 and dibenzo[α ,1]pyrene (DBP) in rainbow trout (Reddy et al., 1996). Xu and Dashwood (1999) found chlorophyllin was a very effective inhibitor of heterocyclic amine-induced colon carcinogenesis in male F344 rats. A clinical trial over 16 weeks involving 180 Chinese individuals living in an area known to have high exposure to dietary aflatoxins

apical to basolateral across Caco-2 monolayers in the presence of increasing molar ratios of CHL. Panels A-B represent the transport of DBP and AFB₁ at concentrations of 1.0 μ M with buffer alone (black diamond) and with CHL present in concentrations of 1.0 (□), 10.0 (Δ), and 100.0 (x) μ M. Experiment in panel A was performed in “nonsink” conditions, while experiment in panel B was “in sink” conditions and is displaced as cumulative transport (*). Values for all timepoints within a treatment group are significantly different from the corresponding control value (Panel a, DBP with CHL at 10.0 and 100.0; Panel B, AFB₁ at 100 μ M $p < 0.05$). (From Mata et al., *Toxicol.*, 196:117–125, 2004. With permission.)

found CHL effectively reduced by 50 percent the median level of urinary excretion of aflatoxin-N⁷-guanine, a DNA adduct biomarker associated with increased risk for liver cancer, compared to the placebo. This study demonstrated the safety and efficacy of using CHL to reduce the genotoxic and cytotoxic effects of aflatoxins in populations at high risk.

Using Caco-2 cell monolayers, Mata and coworkers (2004) suggested one mechanism for the chemopreventive effect of CHL against carcinogens involved reducing the bioavailability of aflatoxin B₁ and DBP. Directly binding CHL with these carcinogens in the intestinal tract could inhibit their transportation from the apical (AP) to the basolateral (BL), as seen in Figure C.25.

Increasing the molar ratios of CHL from 1 to 100 μ M significantly reduced the percent of DBP transported, while 100 μ M CHL was needed to reduce the transport of aflatoxin B₁ approximately 47 percent.

Using cultured fibroblast cells from Chinese hamster lung (V79), Bez et al. (2001) showed chlorophyll *a*, chlorophyll *b*, and chlorophyllin all protected V79 cells from DNA damage induced by methyl methanesulphonate (MMS) by desgenotoxic action and by bioantigenotoxic mechanisms with similar efficiency. Negraes and coworkers (2004) evaluated the anticlastogenicity of chlorophyllin in different phases of the cell cycle by its ability to reverse DNA damage induced by ethyl methane sulfonate. A greater protective effect by CHL against ethyl methyl sulfonate (70–80 percent) was observed during the G2/S phase.

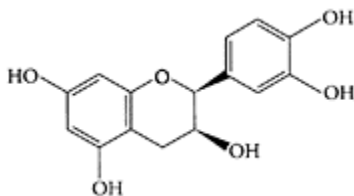
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Chocolate

Chocolate contains fats, sugars, and protein, together with small quantities of magnesium, potassium, calcium, iron, and riboflavin, as well as the stimulant caffeine. The main ingredient in all chocolates is cocoa, derived from beans cultivated in West Africa and Southeast Asia. Among the hundreds of compounds in cocoa are a group of polyphenolic compounds or flavonoids. One group of flavonoids, the procyanidins, account for 35

percent of all polyphenols in cocoa. Procyanidins consist of flavan-3-ol(–) epicatechin (epicatechin) and its polymers (Adamson et al., 1999). Evidence from epidemiological studies



Epicatechin. (Adapted from Babich et al., *Toxicology, in vitro.*, 19:231–242, 2005)

suggest that diets high in polyphenols reduce the risk of cardiovascular disease and related chronic diseases. Chocolate flavonoids are potent antioxidants capable of protecting LDL from oxidation. Richelle and coworkers (1999) demonstrated a physiologically significant increase in plasma levels of epicatechin (0.7 $\mu\text{mol/L}$) in eight healthy male volunteers after consuming 80 g of black chocolates. Wang and coworkers (2000) demonstrated a marked increase in plasma levels of epicatechin in healthy adults 2 h following the consumption of procyanidin-rich chocolates. Rein et al., (2000) showed that a polyphenolic-rich cocoa beverage exerted an aspirin-like effect in 30 healthy subjects by suppressing platelet activation and function, key factors in the development of coronary artery disease. A recent study by Mursu et al. (2004) showed that nonsmoking, healthy young volunteers consuming 75 g daily of dark chocolate and dark chocolate enriched with cocoa polyphenols increased their HDL-cholesterol levels by 11.4 percent and 13.7 percent, respectively. In comparison, the control group consuming white chocolate had a small but significant decrease in HDL cholesterol levels of -2.9 percent. No effect of cocoa polyphenols on lipid peroxidation was observed in the young subjects maintained on the study.

Cocoa procyanidins were found by Mao et al. (1999) to exhibit immunomodulatory effects by inhibiting proliferation and suppressing the production of interleukin-2 and human T-lymphocytes. Carnesecchi and coworkers (2002) further examined the antiproliferative effects of cocoa polyphenols using human colon-cancer cells. The cocoa flavonols and procyanidins caused nonapoptotic cell death and blocked the G2/M phase of the cell cycle. They suggested polyamine biosynthesis as one of the targets affected.

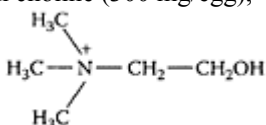
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Choline

Choline is a dietary component essential for normal cell functions. In addition to its incorporation into lecithin and sphingomyelin in cell membranes, it is required for the synthesis of the neurotransmitter, acetyl choline. Choline is also involved in methyl metabolism, as well as for lipid transport and metabolism (Zeisel and Blusztajn, 1994). Eggs are particularly high in choline (300 mg/egg),



mostly in the form of phosphatidylcholine or lecithin. Animal studies have found a choline diet may lead to mental retardation, renal dysfunction, and hemorrhage, as well as bone abnormalities (Fairbanks and Krider, 1945; Handler and Bernheim, 1949; Newberne and Rogers, 1986). During rodent-brain development, there are two periods where choline availability is important. The first is during embryonic days 12–17, and the second is during postnatal days 16–30. Supplementation with choline during these periods is associated with enhanced memory performance (Meck and Williams, 1997, 1999). While no human studies have been conducted so far, Zeisl (2000) suggested that the inclusion of two eggs a day in the diet of pregnant women would be a prudent measure to ensure the dietary requirements of choline are adequately met.

Since hypertension is considered a risk factor for impairments in memory, learning, and attention processes, De Bruin et al. (2003) examined the combined effect of uridine and choline on these cognitive deficits in 5- to 7-month-old spontaneously hypertensive rats (SHR). They found that SHR had significantly impaired visual attention processes

based on the five-choice serial reaction time (5-CSRT), which were normalized following supplementation with uridine and choline. Using the Morris water maze as a measure of spatial learning and mnemonic capabilities, supplementation similarly improved these cognitive disorders in both SHR and normotensive Wistar-Kyoto rats.

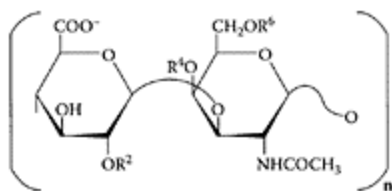
This model could be used to screen compounds that may have therapeutic potential for treating these cognitive disorders.

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Chondroitin sulfate

Chondroitin sulfate (CS) is a group of heteropolysaccharides that are integral components of articular cartilage. They consist of alternate sequences of sulfated or unsulfated D-glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc) residues linked through alternating $[\beta (1 \rightarrow 3)]$ and $[\beta (1 \rightarrow 4)]$ bonds (Scheme C.17). It is used for the treatment of osteoarthritis, a condition in which destructive changes of the osteoarthritic joint leads to pain and functional disability. Current treatment is aimed at management via physical, pharmacological, and surgical approaches. Chondroitin sulfate allows the cartilage to resist tensile stresses by giving the cartilage resistance and elasticity (Muir, 1986). Osteoarthritis is characterized by the destruction of cartilage by degradative enzymes, which are completely inhibited by chondroitin sulfate (Bartolucci et al., 1991; Bassleer et al., 1992). In reviewing the literature, Deal and Moskowitz (1999) concluded there is a sufficient number of studies



	R ²	R ⁴	R ⁶
Δ Di-0S	H	H	H
Δ Di-6S	H	H	SO ₃ ⁻
Δ Di-4S	H	SO ₃ ⁻	H
Δ Di-2, 6 di S	SO ₃ ⁻	H	SO ₃ ⁻
Δ Di-4, 6 di S	H	SO ₃ ⁻	SO ₃ ⁻
Δ Di-2, 4 di S	SO ₃ ⁻	SO ₃ ⁻	H
Δ Di-2, 4, 6 tri S	SO ₃ ⁻	SO ₃ ⁻	SO ₃ ⁻

SCHEME C.17 Structure of chondroitin sulfate disaccharides and compositional properties. (From Sim et al., *J. Chromatogr. B.*, 818:133–139, 2005. With permission.)

suggesting efficacy of glucosamine, chondroitin sulfate, and collagen sulfate equal to that seen in the symptomatic treatment of osteoarthritis using NSAIDs. The effectiveness of chondroitin sulfate and glucosamine was recently reviewed by Hungerford and Jones (2003).

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Chromium

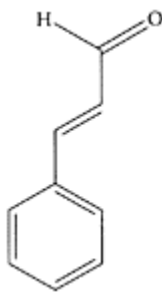
After calcium, chromium is the largest-selling mineral supplement in the United States. Around 10 million Americans use chromium supplements, some for the prevention or treatment of diabetes (Nielsen, 1996). Many studies suggested chromium alleviates severe symptoms associated with diabetes (Jeejeebhoy et al., 1977; Fox and Sabovic, 1998; Ravina et al., 1999). Althuis and coworkers (2002) carried out a systematic review of the literature and a meta-analysis of randomized clinical trials that assessed the impact of dietary chromium supplements on glucose, insulin, and glycated hemoglobin (HbA_{1c}) in healthy subjects and in individuals with glucose intolerance or type 2 diabetes. No association was observed between chromium and glucose or insulin in nondiabetic patients. Only one study of 155 diabetic subjects in China found chromium reduced glucose and insulin and HbA_{1c} levels (Anderson et al., 1997). Althuis and Wittes (2003) defended a number of criticisms made about their study, claiming they only summarized randomized clinical trials that assessed the impact of chromium on glucose, insulin, and Hb A_{1c}. Further studies, however, were recommended, using controlled, randomized clinical trials, to establish the efficacy of chromium in the treatment of diabetes.

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Cinnamaldehyde

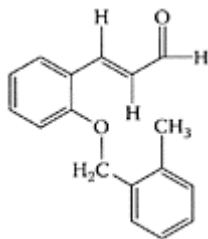
Cinnamaldehyde (CNMA), a major component in cinnamon-bark oil, is used extensively as a flavoring agent in beverages, ice cream, sweets, and chewing gum. Because of its inhibitory effect on farnesyl-transferase activity, Cinnamaldehyde derivatives were screened as potential anticancer agents by Koh and associates (1998). CNMA has been detected in tobacco smoke so that a number of contradictory genotoxicity studies were reported (Neudecker, 1992; Mereto et al., 1994; Stamatii et al., 1999). Imai et al. (2002) investigated the effects of CNMA on lung carcinogenesis using mice initiated with 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK).



Cinnamaldehyde (CNMA). (Adapted from Kim et al., *J. Stored Prod. Res.*, 40:55–63, 2004.)

They found CNMA significantly reduced the multiplicity of lung tumors in CB6F1-TgHras2 (rasH2) and non-Tg female mice. Using an oxidation-sensitive fluorescence probe, DCFH-DA, Ka and coworkers (2003) showed CNMA induced apoptosis in human promyelocytic leukemia HL-60 cells by generation of reactive-oxygen species (ROS). ROS induces mitochondrial permeability transition with the dissipation of the transmembrane potential ($\Delta\psi_m$), triggering the release of cytochrome *c* and the subsequent activation of caspase cascades needed for the onset of apoptosis. This work provided the first evidence on the mechanism of the anticancer effect of CNMA, with further work needed to establish CNMA as a chemopreventive agent for use in cancer treatment.

Jeong et al. (2003) examined the antitumor effect of a more stable synthetic Cinnamaldehyde derivative, CB403, by chemically modifying 2'-hydroxycinnamaldehyde extracted from stem bark. CB403 inhibited the tumor growth of 20 human-cell tumor lines, with SW6720, a human colon-cancer line, being the most sensitive. Further work showed CB403 was cytostatic, inducing mitotic arrest in cancer cells with potential as an anticancer agent.



Structure of CB403. (From Jeong et al., *Biochem. Pharmacol.*, 65:1343–1350, 2003. With permission.)

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Cinnamon

see also Cinnamaldehyde Cinnamon is a widely used flavoring agent in foods. Jarvill-Taylor et al. (2001) showed that methyl hydroxychalcone polymer (MHCP) isolated from cinnamon mimicked insulin by triggering glucose uptake, glycogen synthesis, phosphatidyl-3-kinase dependency, glycogen-synthase activation, and glycogen synthase kinase-3 β activity. Dual treatment with insulin showed synergism was evident between these two compounds. Based on these results, MHCP appeared a good insulin mimetic,

potentially useful in treating insulin resistance. A recent study by Schoene et al. (2005) found water-soluble, polymeric polyphenols from cinnamon inhibited proliferation of hematologic tumor cell lines by altering the proliferative signals regulating progression through the cell cycles.

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Citrus flavonoids

see Hesperidin, Limonene, Naringenin, and Nobiletin Citrus fruit is a rich source of several groups of flavonoids, such as flavanone and flavone glycosides, as well as highly methoxylated flavones and polymethoxylated flavones (Horowitz and Gentili, 1977). The latter were found to exert antiproliferative activities against cancer cells (Kawaii et al., 1999; Iwase et al., 2001). Manthey and Guthrie (2002) isolated polymethoxylated flavones from orange peel and showed they had strong, antiproliferative activities toward human cancer-cell lines.

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Citrus fruit

see also Grapefruit, Lemons, Limes, Mandarins, Oranges, and Tangerines Citrus fruits contain significant amounts of limonene in the peel and smaller amounts in the pulp. Limonene is a monocyclic monoterpene formed by the union of two isoprene molecules. Carbon-4 in limonene is assymetric so that it exists as two optically active forms, *d* and *l*. Limonene has been shown to block and suppress carcinogenic events due to its inhibitory action on certain biochemical pathways in tumor tissues (Elson and Yu, 1994). Monoterpenoids, such as limonene, have been reported to cause tumor regressions with limited toxicity. Limonene significantly reduced azoxymethane-induced colonic aberrant crypt foci in rats fed 5 percent limonene in their drinking water (Kawamori et al., 1996). Limonene is used as a flavor and fragrant agent and is listed as safe (GRAS) in food by the Food and Drug Administration. Manthey and Guthres (2002) showed that poly-methoxylated flavones in citrus exhibited strong antiproliferative activities against six human cell lines, suggesting their use as anticancer agents in humans.

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Club moss

see also Huperzine A An extract from Club moss (*Huperzia serrata*) has been used for centuries in Chinese medicine to treat swelling, fever, and blood disorders. The principal component extracted is a sesquiterpene alkaloid, huperzine A, shown in clinical trials to have neuroprotective properties, which may be beneficial in the treatment of Alzheimer's disease (Zangara, 2003). For further information consult the section on huperzine A.

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Cocoa (*Theobroma cacao*)

see also Chocolate Cocoa is a very rich source of procyanidins, oligomeric flavonoids containing flavan-3-ol units. These compounds are extremely beneficial for their protection against cardiovascular disease by scavenging oxygen and nitrogen species (Rice-Evans et al., 1996). In addition, their ability to inhibit oxidant enzymes has also been reported (Middleton et al., 2000). A recent paper by Mursu et al. (2004) showed healthy, young volunteers consuming 73 g per day of dark chocolate or dark chocolate enriched with cocoa polyphenols had their HDL cholesterol increased by 11.4 percent and 13.7 percent. Schewe and coworkers (2001) reported that epicatechin and cocoa procyanidins inhibited mammalian 15-lipoxygenase, a key enzyme in lipid peroxidation of biomembranes and plasma lipoproteins. Recent research by Schewe et al. (2002) concluded that (–)-epicatechin and its low-molecular-weight procyanidins inhibited both dioxygenase and 5,6-leukotriene A₄ (LTA₄) synthase activities of human 5-lipoxygenase, which could account for the antiinflammatory effects of cocoa products. Inhibition of growth and polyamine biosynthesis by human colonic cancer cells by cocoa powder and extracts was reported by Carnesecchi and coworkers (2002). The procyanidin-enriched extracts significantly decreased ornithine decarboxylase and S-adenosyl-methionine decarboxylase, two key enzymes of polyamine biosynthesis. These results suggested polyamine metabolism may be an important target in the antiproliferative effects of cocoa polyphenols. Yamagishi et al. (2002) reported cocoa liquor proanthocyanidins protected the lungs from 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-induced tumorigenesis, and rat pancreatic carcinogenesis in the initiation stage but not mammary carcinogenesis.

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mutagenesis *in vitro*, and *in vivo* mammary and pancreatic tumorigenesis in female Sprague-Dawley rats, *Cancer Lett.*, 185:123–130, 2002.

Coconut (*Cocos nucifera*)

Coconut is the seed of the coconut palm tree native to the Pacific region of the tropics. It is composed of a thick outer fibrous husk surrounding a hard, stony shell. The lining of the shell, or kernel, contains a white, fleshy, oily area called the meat.

Coconut oil is high in saturated fatty acids. Lauric acid, a 12-carbon saturated acid, accounts for almost 50 percent of the total fatty acids present. Feeding healthy Polynesians coconut oil, butter, and safflower diets, however, still showed cholesterol synthesis was lower on the coconut/safflower-oil diets compared to diets rich in butter (Cox et al., 1998). Padmakumaran Nair and coworkers (1999) reported that human volunteers fed a diet of coconut oil and coconut-kernel protein had lower serum-total- and LDL-cholesterol levels compared to feeding coconut oil alone. The beneficial effects of the kernel protein was attributed to its very low lysine/arginine ratio.

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Coenzyme

Q₁₀ Coenzyme Q₁₀ (CoQ₁₀), a lipid-soluble ubiquinone found naturally in foods, boosts the immune system, enabling the body to defend against viruses and microorganisms. Beef heart and muscle are the richest sources of CoQ₁₀, although it is still present in other tissues. Plants provide varied amounts of CoQ compounds that can be converted to CoQ₁₀ by the liver. Almonds, pistachios, and peanuts are very good sources, providing 10–30 ppm of CoQ₁₀ (Hamid et al., 1995).

FIGURE C.26 Unified Parkinson's Disease Rating Scale (UPDRS) scores. The scores for the total UPDRS (last observation carried forward) are expressed as mean (SEM). Higher

scores indicate more severe features of Parkinson's disease. Results of a test for a linear trend between the dosage and the mean change in the total UPDRS score indicated a trend for coenzyme Q₁₀ to reduce the increasing disability over time ($p=.09$). The score change for the 1200-mg/d coenzyme Q₁₀ group was significantly different from that of the placebo group ($p=.04$). (From Shults et al., *Arch. Neurol.*, 59:1541–1550, 2002. With permission.)

primary effect of CoQ₁₀ was to significantly decrease systolic and diastolic blood pressures and HbA_{1c}. None of these improvements were associated with reduced oxidative stress, as there was no change in the amount of F₂-isoprostanes.

Shults et al. (1997) reported lower levels of CoQ₁₀ in the mitochondria isolated from the plasma of patients suffering from Parkinson's disease (PD). These researchers later showed that oral consumption of dosages of CoQ₁₀ of 400, 600, and 800 mg/day were well-tolerated by patients with PD with significant elevations in blood-plasma levels (Shults et al., 1998). Further work by Shults et al. (2002) showed doses of up to 1200 mg/day were well-tolerated by PD subjects. At the highest dosage, a significant slowing down of PD was observed based on the lower tremor score using the Unified Parkinson's Disease Rating Scale (UPDRS), as shown in Figure C.26. Muller et al. (2003), using a double-blind study, fed much lower doses of CoQ₁₀ to PD patients of 360 mg/day over a four-week period. A moderate improvement in PD symptoms and visual function, as measured with the Farnsworth-Munsell 100 Hue test (FMT), with studies using higher dosages presently under way. Both these studies point to the potential of CoQ₁₀ in the treatment of PD.

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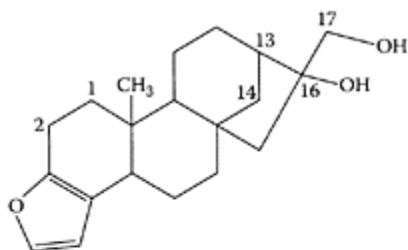
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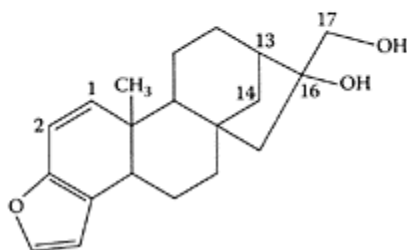
Coffee

Coffee is a popular beverage that is consumed worldwide. Epidemiological studies on the relationship between coffee and cancer suggests that moderate coffee consumption (2–5 cups/day) does not represent a risk to humans (Schiller et al., 2001a). Many studies, in fact, showed an inverse relationship existed between certain cancer risks and coffee consumption (Nishi et al., 1996; Giovannucci, 1998; Inoue et al., 1998). Meta-analysis of five cohort and 12 case-control studies all pointed to a significant inverse relationship between coffee consumption and colorectal cancer (Giovannucci et al., 1998). The chemoprotective effect of coffee has been demonstrated in experimental animals by its inhibitory effects on carcinogens, nitrosamines, and 1,2-dimethyl-hydrazine (Gershbein, 1994; Nishikawa et al., 1986). Anticarcinogenic effects were also demonstrated for green, as well as roasted, coffees in animal models treated with 7,12-dimethyl-benz[α]anthracene (Miller et al., 1988, 1993).

Caffeine and polyphenols, such as chlorogenic acid and their degradation products, were considered to be among the compounds responsible for the chemoprotective properties of coffee (Stadler, 2001; Schilter et al., 2001b). A specific lipid fraction in coffee was associated with its ability to inhibit DMBA-induced cancer in rats, mice, and hamsters (Lam et al., 1982; Wattenberg et al., 1986; Miller et al., 1991). This fraction contained diterpenes, cafestol, and kahweol C+K.



C



K

Structures of coffee diterpenes cafestol (C) and kahweol (K). (From Cavin et al., *Food Chem. Toxicol.*, 40:1155–1163, 2002. With permission.)

The difficulty in isolating these components separately, combined with the instability of kahweol, led to studies using a mixture of these two compounds. Cavin et al. (2002) showed the diterpene mixture prevented DNA binding with aflatoxin B1 and the environmental carcinogen, benzo[a]-pyrene(B[α])P in rat hepatocyte cultures in a dose-dependent response (Figure

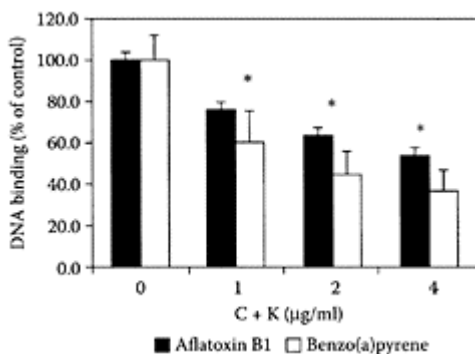


FIGURE C.27 Dose-dependent effect of cafestol and kahweol (C+K) on the

formation of aflatoxin B₁ metabolites and benzo[α]pyrene-induced DNA adducts *in vitro*. Results presented are means obtained from five experiments with two independent cultures per treatment (\pm S.D.). These are expressed as the percentage of the mean value derived from control cultures. In control, the absolute binding rate (equal to 1005) were in average 6.5 pmol AFB₁ and 4.5 pmol B[α]P/mg DNA, respectively. *Significantly different from control rat primary hepatocytes ($p < 0.05$) using the Student's t-test. (From Cavin et al., *Food Chem. Toxicol.*, 40:1155–1163, 2002. With permission.)

C.27). These diterpenes also reduced the genotoxicity of several other carcinogens, including 7,12-dimethylbenz[*a*]-anthracene (DMBA), aflatoxin B₁, and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), using animal models and cell cultures. Chemoprotective effects were attributed to induction of conjugating enzymes (e.g., glutathione *S*-transferases and glucuronyl *S*-transferases), increased protein expression involved in antioxidant defense (e.g., γ -glutamyl cysteine synthetase and heme oxygenase-1), and inhibition of expression or activation of cytochromes P450, the latter normally involved in activation of the carcinogen. The molecular mechanism appeared similar to many cancer-chemopreventive blocking agents and involves the Nrf2 transcription factor through regulation of cis-acting, antioxidant-responsive-element (ARE)-driven gene expression. Further work by Cavin and coworkers (2003) showed C+K inhibited B[*a*]P-DNA adduct formation in primary rat hepatocytes and human bronchial Beas-2B cells. Huber et al. (2003) showed that K/C and Turkish coffee (cafestol alone) both increased hepatic DNA repair protein O⁶-methylguanine-DNA methyl-transferase (MGMT) in a dose-dependent manner. The increase in MGMT expression provides new insight regarding the antimutagenic/anticarcinogenic potential of these coffee components.

Van Dam and Feskens (2002) reported coffee consumption may reduce the risk of type 2 diabetes mellitus. Of 17,111 Dutch men and women between the ages of 30–60, those drinking a minimum of seven cups of coffee a day were 0.50 (95 percent CI 0.35–0.72, $p = 0.0002$) times as likely to develop diabetes mellitus compared to those drinking two or fewer cups. Components in coffee that could contribute to this effect are caffeine, chlorogenic acid, and magnesium.

Tavani and coworkers (2003) observed an inverse relationship between coffee intake and risk of oral, pharyngeal, and esophageal cancers. A total of 749 and 395 cases were

studied suffering from oral/pharyngeal and esophageal cancers, respectively. The multivariate odds ratio (OR) for those drinking more than three cups of coffee/day compared to one cup of coffee/day were 0.6 (95 percent CI 0.5–0.9) for oral/pharyngeal and 0.6 (95 percent CI 0.4–0.9) for esophageal cancer, irrespective of age, sex, education, and alcohol consumption. These results suggested coffee consumption may decrease the risk of oral/pharyngeal and esophageal cancers.

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Colostrum

The first mammary gland fluid secreted by mammals during the first four days after birth is known as the colostrum. Besides the major nutritional components normally associated with milk, colostrum contains many minor bioactive components capable of treating many human diseases. For example, the presence of immunoglobulins in the colostrum is extremely important, as these antibodies play a crucial role in immune protection. Casswall et al. (1998) showed that oral immunoglobulins from bovine colostrum effectively treated *Helicobacter pylori* infections in infants in rural Bangladesh. Bovine colostrum, particularly Ig_G, could provide an immunological supplement in infant formula and other hyperimmune foods (Dominguez and coworkers, 1997). A range of growth factors present include insulin-like growth hormone (IGF) and transforming growth factor (TGF), as well as lactoferrin and lactoperoxidase. For a long time, breast-fed babies were known to be resistant to certain types of infections, particularly intestinal disorders (Jatsky and coworkers, 1985). Among the immune factors in colostrum is an iron-binding protein with antibacterial and antiviral properties, lactoferrin (Wilson, 1997). Purified lactoferrins were shown to inhibit the effects of HIV in cells and fibroblasts (Swart et al., 1998). Colostrum provides a wide range of benefits, including preventing gastrointestinal damage from nonsteroidal, anti-inflammatory drugs (NSAIDs). A number of commercial products are available. An excellent review of colostrum was published by Uruakpa and coworkers (2002).

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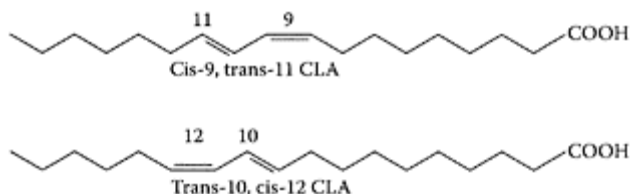
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Conjugated linoleic acid

Conjugated linoleic acid (CLA), a class of positional and geometrical conjugated isomers of linoleic acid containing two double bonds separated by a single bond was first reported in dairy products and beef (Pariza et al., 2001). The main isomers identified in foods are *cis*-9, *trans*-10 (c9, t11) and *trans*-10, *cis*-12 (t10, c12) CLA. CLA has some unique chemoprotective properties (Belury, 1995). For example, it has been reported that CLA lowered total body fat and increased lean body mass (Blankson et al., 2000; Delany et al., 1999). In addition, a number of other health benefits have been associated with CLA, including chemopreventative effects against tumors (Visonneau et al., 1996). CLA is also reported to lower cholesterol and to be antiatherogenic. Wilson and coworkers (2000) showed a diet containing conjugated linoleic acid fed to hypercholesterolemic hamsters over 12 weeks significantly reduced the development of early aortic atherogenesis more effectively than linoleic acid, due possibly to changes in the susceptibility of LDL cholesterol to oxidation. Subsequent work by Kritchevsky et al. (2002) showed that a diet containing as little as 0.05 percent CLA reduced the severity of atherosclerosis in the aortic arch of hamsters by 20 percent and in the thoracic aorta by 8 per-cent. Increasing the level of CLA in the diet was accompanied by a corresponding decrease in the severity of atherosclerosis. Based on the effectiveness in the hamster diet of 0.5 percent CLA level, these researchers felt that a normal human diet could contain an effective level of dietary CLA.

Using a 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)-induced rat mammary carcinogenesis model, Futakuchi and coworkers (2002) reported conjugated linoleic acid from safflower or perilla oil decreased carcinogenesis in the postinitiation period, with inhibition of cell proliferation. The antiproliferative effects of two commercial preparations of CLA, containing isomers (c9, t11-CLA, c9, c11-CLA, and t10, c12-CLA), were examined by Palombo et al. (2002) using human colorectal (HT-29, MIP-101) and prostate (PC3) carcinoma cells. Both the type and concentration of individual CLA isomers determined their antiproliferation effects. The greatest potency against proliferation of colorectal-cancer cells was observed for t10, c12-CLA, while c9, t11 and t10, c12 isomers were only moderately effective against prostate-cancer cells.



CLA isomers. (From Evans et al., *J. Nutr. Biochem.*, 13:508–516, 2002. With permission.)

TABLE C.22

Effect of CFA-S on Cell Proliferation of Mammary Adenocarcinoma and Colon Epithelium

Treatment	Number of Lesions Examined	PCNA¹ Positive Index (%) Mammary Adenocarcinoma	Colon Epithelium
(+) Control	10	7.5+4.2	28.8+5.8
(+) CFA-S 0.01%	10	5.7+2.5	21.7+5.7*
(+) CFA-S 0.05%	10	6.3+3.4	22.3+4.7*
(+) SFA-S 0.1%	10	6.4+2.8	22.4+6.0*
(+) CFA-S 1%	10	4.7+2.4	19.7+5.5**
(+) CFA-2%	10	6.9+3.6	23.4+5.6*

¹PCNA-Proliferating cell nuclear antigen. * $p < 0.05$, ** $p < 0.01$ vs. control values.

Source: Cheng et al., *Cancer Lett.*, 196:161–168, 2003. With permission.

Kimoto et al. (2001) reported that 1 or 0.1 percent CLA safflower oil (CFA-S) suppressed mammary carcinogenesis in a two-stage model in female rats. Recent work by Cheng et al. (2003) showed that the optimal level for inhibiting carcinogenesis in rat mammary glands and colon, induced by 1,2-dimethyl-benz[α]-anthracene (DMBA) and 1,2-dimethylhydrazine (DMH), was 1 percent (Table C.22).

A recent study by Albers and coworkers (2003) showed that supplementation with a 50:50 CLA mixture (c9, t11+t10, c12) enhanced the immune system of healthy males by increasing the sero-protection rate following hepatitis B vaccination. This could be beneficial to those individuals who are slow or low responders to the vaccination. Further research is needed, however, to determine whether similar effects are accrued following exposure to infection. A recent review on conjugated linoleic acid by Wahle et al. (2004) is recom- mended.

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Coriander (*Coriandrum sativum* L.)

Coriander is an annual herb with delicate, bright leaves. Its seeds are used to flavor foods, while its aromatic oil is used in cream lotions and perfumes. Anilakumar et al. (2001)

examined the effect of feeding 10 percent coriander-seed powder on hexachlorocyclohexane-induced oxidative stress in rat livers. The antioxidant properties of coriander-seed powder were evident by a reduction in conjugated dienes, hydroperoxides, and malondialdehyde in the liver. Prefeeding coriander-seed powder appeared to counteract the effect of hexachlorocyclohexane by enhancing the hepatic oxidant system. Guerra et al. (2005) recently isolated five carotenoids, β -carotene, β -cryptoxanthin epoxide, lutein-5,6-epoxide, violaxanthin, and neoxanthin, from an ether extract of coriander. Of these, β -carotene represented 61.4 percent of the total carotenoids isolated. The antioxidant activity of the crude fraction was much greater than the individual fractions, suggesting synergism between the individual fractions. Delaquis et al. (2002) compared the antimicrobial activity of a number of essential oils, including coriander. Distilled fractions of purified coriander oil proved far more effective in inhibiting test microorganisms compared to the crude oil. Several purified fractions were obtained, with the more potent fraction containing a mixture of α -pinene (89.4 percent) and camphene (8.5 per-cent).

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Corn bran

Corn bran, produced by dry milling, was shown by several researchers to lower cholesterol (Shane and Walker, 1995; VidalQuintanar et al., 1997). The particle size of corn bran was shown by Ebihara and Nakamoto (2001) to affect plasma cholesterol, fecal output, and cecal fermentation in rats. A fiber-free diet was compared to a corn-bran (50 g/kg) diet, ranging in different particle sizes, from 105 to 500 μ m. A reduction in particle size was accompanied by a decrease in plasma cholesterol, fecal wet weight, and fecal bulking effect in the rats. Examination of rat liver showed a corresponding increase in cholesterol concentration, cecal-wall weight, and wet weight of cecal content, together with higher levels of total organic acids in the cecal, such as acetic and n-butyric acids.

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Corn-fiber oil

Corn-fiber oil is a by-product of dry milling of corn. Wilson and coworkers (2000) found that the oil extracted from corn-oil fiber reduced plasma and hepatic cholesterol and increased fecal cholesterol excretion in hamsters fed a hypercholesterolemic diet, to a much greater degree than corn oil. Corn-oil diets containing soy sterols or stanols exhibited similar effects on plasma cholesterol levels and cholesterol excretion to that of corn-fiber oil.

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Corn oil

Corn oil is a premium-quality oil rich in ω -6 fatty acids. Linoleic acid (C18:2 ω -6) accounts for approximately 60 percent of the total fatty acids in corn oil, while oleic acid (C18:1 ω -9) comprises around 26 percent. Many studies have shown corn-oil diets fed over a long duration lower total and LDL cholesterol, while HDL-cholesterol remained unchanged (Iacono and Dougherty, 1991). The greater-than-expected lowering of cholesterol by corn oil was explained, in part, due to the presence of naturally occurring plant sterols in the oil (Mattson et al, 1982; Laraki et al., 1993). Corn oil has been shown to significantly lower elevated blood pressure (Iacono and Dougherty, 1993) and reduce the progression of diabetic angiopathy in adult onset diabetes mellitus (Houtsmuller et al., 1982). However, corn oil appears to increase the rate of growth of established tumors. Rusyn and coworkers (1999) showed corn oil rapidly activated the nuclear factor- κ B (NF- κ B) in Kupffer cells through an oxidant-dependent mechanism. This in turn triggers

the production of the tumor necrosis factor α (TNF- α). An earlier study by Gonzalez et al. in 1991 compared corn oil (high in ω -6 fatty acids) with fish oil (high in ω -3 fatty acids) on the growth of human breastcarcinoma cell lines. Unlike fish oil, which significantly increased lipid peroxidation and decreased tumor volume, corn oil increased human breast-carcinoma volume.

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Cranberry fruit

Cranberry (*Vaccinium macrocarpon* Ait. Ericaceae), a native fruit in North America, has been reported to provide health benefits, such as preventing bacterial adhesion in urinary-tract infections of *Escherichia coli*

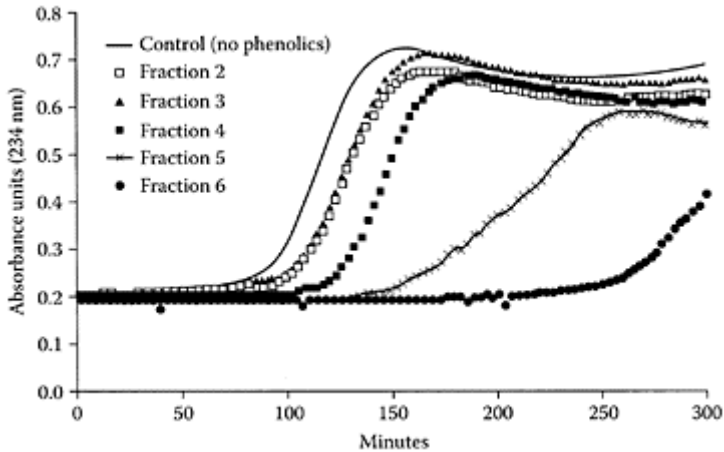


FIGURE C.28 Effect of cranberry flavonoid fractions on lag time of Cu^{2+} -induced LDL oxidation. Histograms show the mean ($n=3$) and the error bars the SEM. Significant differences ($p<0.05$) between treatment means are denoted by different letters above the error bars. Fraction 2 contained a hydroxycinnamic acid peak and several anthocyanins. Fractions 3 and 4 also contained flavonoids. Fraction 4 also contained a few lowmolecular-weight proanthocyanidins. Fractions 5 and 6 both contained proanthocyanidins. (From Porter et al., *J. Sci. Food Agric.*, 81:1306–1313, 2001. With permission.)

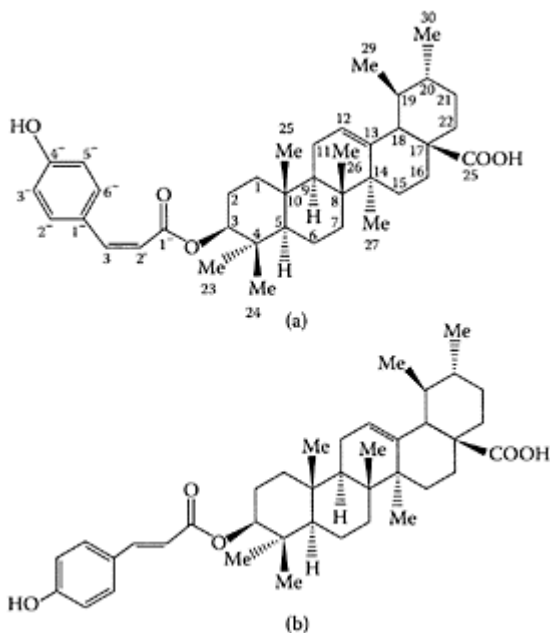
and stomach ulcers (Burger et al., 2000; Foo et al., 2000), inhibiting lipoprotein oxidation (Wilson et al., 1998), and exhibiting anticancer properties (Bomser et al., 1996). Many of these health benefits are associated with its phenolic content, which was shown to be highest per serving among 20 fruits examined and ranked sixth in antioxidant capacity (Vinson et al., 2001). Yan and coworkers (2002) found the highest radical-scavenging activity was associated with cranberry extract. Their flavonol glycosides had similar or superior antioxidant activity to vitamin E when assayed using either the diphenyl-2-picrylhydrazyl radical-scavenging method or the low-density lipoprotein oxidation

system. Cyanidin 3-galactoside stood out by its superior antioxidant activity to flavonoids and vitamin E using both methods.

Porter and coworkers (2001) showed six cranberry phenolic fractions inhibited Cu^{2+} -induced low-density (LDL) oxidation in human serum (Figure C.28). Only several fractions (5 and 6) that contained proanthocyanidins significantly increased the LDL-oxidation lag time. One of these fractions contained trimers through to heptamers, with the more potent fraction containing pentamers through to nonamers. The anticancer activity of cranberries was attributed to inhibition of ornithine decarboxylase (ODC) by flavonol glycosides and proanthocyanidins (Kandil et al., 2002). This enzyme was previously shown to be involved in tumor proliferation. Two cranberry extracts were reported by Guthrie (2000) to inhibit the proliferation of breast-cancer cells. Yan et al. (2002) also reported the selective inhibition of two of seven tumor-cell lines by a methanolic extract from cranberry fruit ranging from 16–125 $\mu\text{g/mL}$. Murphy et al. (2003) identified several new triterpenoid hydroxycinnamates from a bioactive cranberry fruit fraction, *cis*-(1) and *trans*-(2) 3-*O-p*-hydroxycinnamoyl ursolic acids (Scheme C.18). Both were found to inhibit tumor-cell growth. The greatest antitumor activity, however, was associated with the *s* isomer(1), resulting in a 50 percent growth inhibition in MCF-7 breast, ME 180 cervical, and PC3 prostate-tumor lines in the presence approximately 20 μM . Based on these results, cranberries clearly contain an array of compounds with potential health benefits.

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SCHEME C.18 Bioactive triterpenoids, *cis*- (a) and *trans*- (b) 3-*O*-p-hydroxycinnamoyl ursolic acids. (From Murphy et al., *J. Agric. Food Chem.*, 51:3541–3545, 2003. With permission.)

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Cranberry juice

Sobota (1984) first reported that fresh cranberry juice prevented bacterial adhesion, a prerequisite for the development of urinary-tract infection. Later studies by Ahuja et al. (1998) showed cranberry juice had no antibacterial activity but inhibited adhesion by *P. fimbriae*. The substances in cranberry juice responsible were shown to be the condensed tannins, proanthocyanidins. Howell et al. (1998) found cranberry proanthocyanidins prevented adherence of uropathogenic P-fimbriated *Escherichia coli* to the urinary tract. The effect was detectable in the presence of 10–50 µg/mL proanthocyanidins. Examination of senior residents (mean age 78.5 years) in a long-care facility by Avorn and coworkers (1994) found that consumption of 300 mL of a cranberry cocktail significantly decreased infections by bacteriuria and pyuria. The protective role of cranberry juice was further supported by Haverkorn and Mandigers (1994), who found fewer cases of bacteriuria in patients given cranberry juice (15 mL) diluted with water twice a day for a month. Based on clinical studies carried out to-date, Lowe and Fagelman (2001) encouraged supplementing cranberries, as juice, concentrate, or in cocktail formulations, because of its beneficial effect in preventing urinary-tract infections. Burger et al. (2000) also showed cranberry juice inhibited adhesion of *Helicobacter pylori*, a major cause of gastrointestinal infections in humans.

Pedersen and coworkers (2000) reported an increase in plasma antioxidant capacity following consumption of cranberry juice.

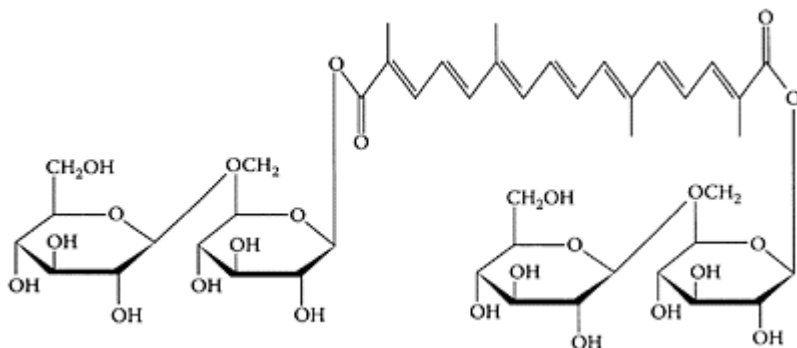
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Crocin

see also Saffron The pistils of *Crocus sativus* L. have been used in traditional Chinese medicine to treat disorders of the central-nervous system. Extracts obtained from *Crocus sativus* were shown to prevent tumor



Crocin. (From Soeda et al., *Life Sci.*, 69:2887–2898, 2001. With permission.)

formation, atherosclerosis, and hepatic injury (Gainer and Jones, 1975; Salomi et al., 1991; Wang et al., 1991). Ethanol is well-known to impair brain functions, such as learning and memory. Research conducted on *Crocus sativus* L. showed that components in this extract antagonize ethanol-induced memory impairment. The component responsible was identified as crocin (crocetin di-gentiobiose) (Sagiura et al., 1995). Subsequent work by Abe and coworkers (1998) showed crocin selectively antagonized the inhibitory effect of ethanol on *N*-methyl-D-aspartate (NDMA) receptor-mediated responses in hippocampal neurons, suggesting it may be useful for treating brain disorders. The pathology of neurodegenerative diseases is associated with unexpected neuron deaths occurring during a stroke (Crowe, 1997), trauma (Hill et al., 1995), or in the brains of Alzheimer's patients (Pettmann and Henderson, 1998). A possible

therapeutic strategy for treating these disorders would be to prevent neuronal-cell death as overexpression of the tumor necrosis factor (TNF- α) has been implicated in the pathogenesis of Alzheimer's disease (Fillit et al., 1991) and Parkinson's disease (Boka et al., 1994). Using neuronally differentiated PC-12 cells, Soeda and coworkers (2001) showed that in cells treated with 10 μ M crocin, the normal features of cell death were not evident due to suppression of TNF- α -induced expression Bcl-2 proteins, which triggers signals that activate caspase-3 and the development of apoptosis.

Escribano and coworkers (1996) compared the effectiveness of crocin, safranal, and picrocrocin, compounds present in saffron (*Crocus sativus* L.), on their ability to inhibit the growth of human cancer cells. A 50 percent inhibition of cell growth (LD₅₀) was observed with 3 mM crocin in which cells showed wide cytoplasmic vacuole-like areas, reduced cytoplasm, cell shrinkage, and pyknotic nuclei. These researchers viewed crocin as one of the more promising compounds in saffron as a cancer therapeutic agent.

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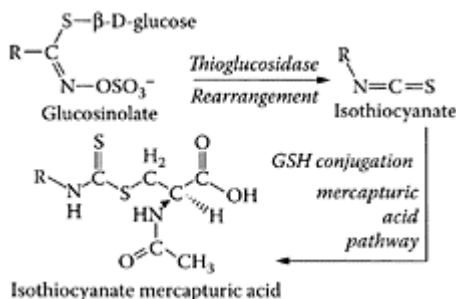
Cruciferous vegetables

see also Brassica Cruciferous vegetables, including cabbages, broccoli, Brussels sprouts, radish, mustard, and cress, are all high in glucosinolates. When these vegetables are cut, ground, or damaged, the glucosinolates are hydrolyzed by an enzyme, myrosinase, producing biologically active isothiocyanates (ITC) and indoles. There appears to be an inverse relation between cruciferous vegetables and the risk of cancer (Verhoeven et al., 1997; Talalay and Fahey, 2001). Lampe and Peterson (2002) reviewed the chemoprotective effects of the high glucosinolate content of cruciferous vegetables and their metabolites, ITC and indoles, in relation to cancer prevention. Since isothiocyanates are strong inhibitors of phase I enzymes but inducers of phase II enzymes (Zhang and Talalay, 1998), cruciferous vegetables were considered cancer chemopreventors, which was confirmed in human-intervention studies (Bogaards et al., 1998; Nijhoff et al., 1995). Steinkeller et al. (2001) presented evidence that cruciferous vegetables and their constituents protect against bioactivation of DNA-reactive dietary carcinogens. Induction of uridinediphospho-glucuronosyl transferase (UDPGT) appeared the protective mechanism involved against heterocyclic amines by the cruciferous vegetables.

Isothiocyanates formed in the digestion of cruciferous vegetables are conjugated with glutathione and excreted in the urine as their corresponding mercapturic acids (Scheme C.19). Vermeulen and coworkers (2003) developed an efficient method for monitoring the intake and action of isothiocyanates by measuring the corresponding mercapturic acids as biomarkers.

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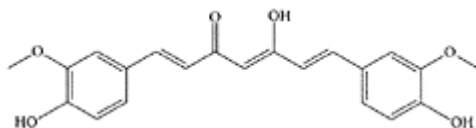
SCHEME C.19 Glucosinolates enzymatically hydrolyzed to isothiocyanates are then conjugated to glutathione, followed by excretion as mercapturic acids in the urine. (From Vermeulen et al., *J. Agric. Food Chem.*, 51:3554–3559, 2003. With permission.)

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Curcumin

Curcumin, the yellow pigment from turmeric, was shown to be a potent inhibitor of radiation-induced initiation of mammary tumors in rats (Inano et al., 2000). The inhibitory effect of curcumin on telomerase reverse-transcriptase (hHRT) activity was reported by Ramachandran and coworkers (2002) in MCF7 breast-cancer cells. This effect was dose dependent, with 93.4 percent inhibition in the presence of 100 μ M curcumin. The inhibition of telomerase activity appeared to involve



Curcumin. (From May et al., *Anal. Biochem.*, 337:62–69, 2005. With permission.)

down-regulating hHERT expression by the breast-cancer cells. The ability of curcumin to inhibit the formation of the Fos-Jun-DNA complex led Hahm and coworkers (2002) to synthesize 12 symmetrical curcuminoids. One of these, BJC005, proved to be 90 times more effective than curcumin and more potent than momordin, a potent Fos-Jun inhibitor.

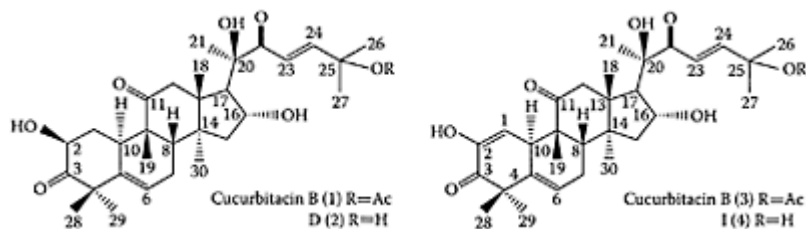
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Cucurbita andreana

In Latin America, the flowers, leaves, and vine tips of cucurbita spp. are widely consumed, because they exhibit a wide range of biological activities in plants and animals. Early work identified a group of terpenoid compounds or cucurbitacins present (Metcalf et al., 1982; Miro, 1995). These are highly oxygenated, tetracyclic triterpenes containing a cucurbitane skeleton characterized by a 19-(10→9 β)abeo-10 α -lanost-5-ene. Some of these cucurbitacins were shown to exhibit antiinflammatory effects linked possibly to inhibition of cyclooxygenase (COX) enzymes.

A recent study by Jayaprakasam et al. (2003) showed these cucurbitacins (B, D, E, and I) exhibited potent anticancer activity, as well as



Cucurbitacins. (From Jayaprakasam et al., *Cancer Lett.*, 189:11–16, 2003. With permission.)

inhibited COX-2 enzyme. Further research is needed to determine the toxicity of these compounds.

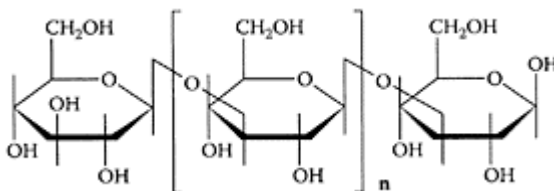
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Curdlan

Curdlan, a β 1,3-glucan synthesized by *Alcaligenes faecalis* var. *myxogenes*, was reported to have a number of health benefits (Jezequel, 1998). Shimizu et al. (1999) found rats fed a curdlan diet produced lower cecal pH accompanied by the release of large amounts of short-chain fatty acids (SCFA) and a lower ratio of fecal secondary bile acids. The anticancer properties of curdlan were further demonstrated by Shimizu and coworkers (2002), who showed a diet containing 5 percent curdlan significantly reduced dimethylhydrazine (DMH)-induced aberrant crypt foci development in Sprague-Dawley rats. Curdlan proved more effective than either cellulose or gellan gum in reducing the number of aberrant crypt foci (Figure C.29).

A search for antihuman immunodeficiency virus (HIV) agents to treat AIDS that did not have serious side effects led to the identification of a polysulphonated polysaccharide, curdlan sulfate (Molla et al., 1996). *In vitro* studies showed the anti-HIV activity in sulfated curdlan was due to its effects on viral replication by preventing binding to HIV virions to CD4⁺ lymphocyte cells and syncytium formation (Baha et al., 1988). Further research showed a synthetic



Curdlan. (From Jezequel, *Cereal Foods World*, 43:361–364, 1998. With permission.)

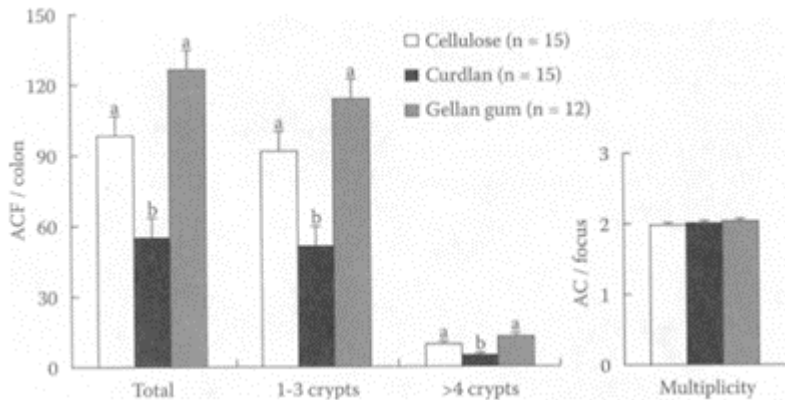


FIGURE C.29 Numbers of DMH-induced aberrant crypt foci (ACF) of rats fed experimental diets. Bars are means \pm SEM. Each bar with different letters indicates differences from Tukey's test ($p < 0.05$). (From Shimizu et al., *Nutr. Res.*, 22:867–877, 2002. With permission.)

curdlan sulfate exhibited high anti-HIV activity and low toxicity. A series of phase I/II clinical tests conducted on curdlan sulfate in the U.S.A. between 1992 and 1996, however, found no significant improvements in patients given intravenous doses of 100 to 300 mg over the short term (Gordon et al., 1997). Jeon and coworkers (2000) analyzed NMR signals for polymeric interactions between curdlan sulfate and an HIV protein but obtained precipitates rather than gels, which did not yield any structural information. Further work is needed to establish the efficacy of curdlan sulfate, based on its anti-HIV properties, as a long-term therapy for AIDS.

A recent double-blind, placebo-controlled study on patients suffering from severe and severe/cerebral malaria by Havlik et al. (2005) examined the efficacy and safety of using curdlan sulfate as an adjunct medication with conventional therapy, artesunate. Curdlan sulfate was found to reduce the severity of cerebral malaria by shortening the fever-clearance period. No additional complications were observed with curdlan sulfate, such as renal failure or pulmonary oedema, as it appeared to be well-tolerated. However, the small number of patients in this study suggests further clinical trials with a larger number of patients is warranted.

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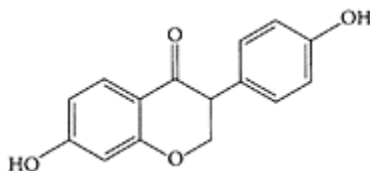
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D

Daidzein

Daidzein, one of the major isoflavone aglycones in soybean, is usually present in the form of its β -glucoside, daizin. While isoflavones are bitter and astringent, they all exhibit antihemolytic, antioxidative, antifungal, estrogenic, and antitumoral properties (Naim et al., 1976; Farmakaladis et al., 1985; Miyazawa et al., 1999). It is the antioxidant properties of isoflavones that are generally attributed for their anticancer properties (Ruiz-Larrea et al., 1997; Stoll, 1997). The free-radical-quenching properties of daidzein prevented the formation of oxidized DNA, 8-hydroxy-2'-deoxy-guanosine, in cells and DNA exposed to oxidants or in men



Daidzein. (From Peng et al., *Food Chem.*, 87:135–139, 2004. With permission.)

consuming 1 liter of soy milk daily over a four-week period (Giles and Zwei, 1997; Mitchell and Collins, 1999). Djuric et al. (2001) conducted a pilot study in which a combination of daidzein and genistein, in the form of a tablet, reduced endogenous oxidative DNA damage, as measured as 5-hydroxymethyl-2'-deoxyuridine (5OhmdU), in the blood cells of men and women kept on a twice-daily regimen of 50 mg isoflavone tablets for three weeks. After one week of supplementation, there was a 61 percent decrease in 5OhmdU in the blood cells of women, while it took three weeks before there was a corresponding decrease of 47 percent in men. This reduction in oxidative damage was considered a possible mechanism for its anticancer properties. Guo and coworkers (2004) showed daidzein had a biphasic effect on the cell growth of a human colon-cancer cell line LoVo. At low concentrations ($<1 \mu\text{M}$) daidzein stimulated growth, while at high concentrations ($>10 \mu\text{M}$) cell growth was inhibited in a dose-dependent manner. Inhibition of cell growth was characterized by cell-cycle arrest at G0/G1, DNA fragmentation, and enhanced caspase-3 activity.

Daidzein belongs to the family of diphenolic compounds with structural similarities to natural and synthetic estrogens and antiestrogens (Kurzer, 1999). It binds to estrogen receptors, although somewhat weakly compared to estradiol. The estrogenic properties of phytoestrogens, such as daidzein, are thought to prevent bone resorption and increase bone density. This is particularly important, as osteoporosis is generally linked to decrease in steroid production associated with menopause in women. Osteoblasts, the most important cells in bone tissues, are critical to bone formation and bone density. Daidzein was shown to stimulate protein synthesis, alkaline-phosphatase activity, and DNA content in an osteoblast MC3T3-E1 cell (Sugimoto and Yamaguchi, 2000), as well as significantly increase alkaline-phosphatase activity, DNA, and calcium content in bone tissues (Gaio and Yamaguchi, 1999). Jia et al. (2003) showed that daidzein stimulated osteoblast growth in newborn Wistar rats at various stages (from osteoprogenitors to terminally differentiated osteoblasts). For example, the production of osteocalcin, a specific marker protein for the terminal differentiation of osteoblasts, was significantly increased in the presence of daidzein in a concentration-dependent manner (Figure D.30). In addition, daidzein regulated bone-morphogenetic protein (BMP) by significantly increasing BMP2RNA and protein synthesis in osteoblastic cells cultured *in vitro*.

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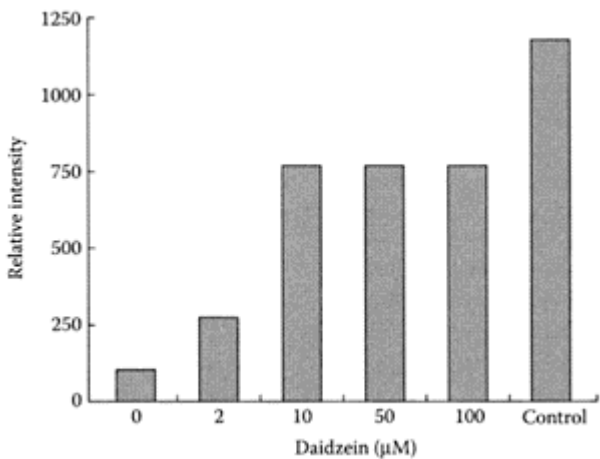


FIGURE D.30 Effect of daidzein on osteocalcin synthesis in osteoblastic cells incubated for two days. Each value is the mean \pm of six dishes. (*) $p<0.05$, compared to the control without daidzein. (Adapted from Jia et

al., *Biochem. Pharmacol.*, 65:709–715, 2003. With permission.)

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Dairy products

Epidemiological studies identified a close relationship between the intake of dairy products and blood pressure. This is related to such minerals as calcium and potassium, which are inversely linked to blood pressure and the incidence of hypertension (McCarron, 1989). Since dairy products provide 70–75 percent of total dietary calcium intake, these studies identified higher arterial pressure or hypertension in populations or individuals with low dairy and low calcium, magnesium, and phosphorus intakes. A multicenter, randomized clinical trial by the National Heart, Lung, and Blood Institute of the United States entitled “Dietary Approaches to Stop Hypertension” (DASH) compared

a typical American diet low in fruits, vegetables, and dairy products with the DASH diet, a low-fat dairy products and a high fruit-and-vegetable diet (Appel et al, 1997). This was a fairly definitive study, which showed those individuals with high blood pressure or hypertension clearly benefited from the DASH diet. Overall, at least three servings of low-fat dairy products were recommended per day by the Institute of Medicine for adults below 50 years of age taking 1000 mg calcium per day, while those over 50 needed four servings of low-fat dairy products and 1200 mg of calcium per day (Standing Committee on the Scientific Evaluation of Dietary References, 1997). A summary of the biomedical literature by Miller et al. (2000) covers the benefits of dairy products, particularly in relation to blood pressure. A recent paper by McCarron and Heany (2004) estimated that if Americans simply increased their intake of dairy foods to the current recommendation of three to four servings per day, the reduction in disease burden could result in a substantial medical savings of more than \$200 billion over a five-year period.

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Dandelion

The dandelion (*Taraxacum officinale*), considered by most homeowners to be a nuisance plant, is a common plant grown commercially in Europe and the United States. Its choleric, antirheumatic, and diuretic properties have made dandelions an herbal medicine (Bradley, 1992; Bissett, 1994). The bitter substances identified in dandelion thought to be responsible for its therapeutic properties were sesquiterpene lactones, taxacoside triterpenes, phytosterols, phenolic acids, flavonoids, vitamins, and minerals (Racz-Kotilla et al., 1974; Kuusi et al., 1985; Wichtl, 1994; Williams et al., 1996). Mascolo et al. (1974) reported leafdandelion extracts exhibited anti-inflammatory properties in experimental animals. Subsequent research by Cristinf and coworkers (1996) showed that aqueous dandelion extracts containing cinnamic acids and coumarins had antitumor activity. Cho et al. (2002) examined any possible diuretic effects exerted by aqueous extracts of dandelion leaves in streptozotocininduced diabetic male Sprague-Dawley rats.

Since diabetes-related complications are associated with oxidative stress, these researchers examined the effect of the dandelion-leaf extracts on hepatic antioxidant enzyme activities and lipid profiles in the experimental animals. The most notable differences were observed in serum and hepatic lipids, as shown in Table D.23.

Supplementation with dandelion extract (DWE) lowered total cholesterol and triglycerides, while raising HDL-cholesterol in the diabetic rats. In addition, treatment with DWE significantly lowered the atherogenic index. These results suggested that DWE treatment could be useful as antioxidant therapy to correct hyperglycemia and protect against free radicals. Further work is needed to identify the specific components responsible.

TABLE D.23

Effect of Dandelion Water-Extract Supplementation on Serum and Hepatic Lipids in Diabetic Rats¹

	Nondiabetic	Diabetic	Diabetic-DWE
Serum			
Total Cholesterol (mmol/L)	2.41±0.07 ^a	3.10±0.15 ^b	2.44±0.31 ^a
HDL Cholesterol (mmol/L)	0.81±0.06 ^a	0.33±0.04 ^c	0.67±0.07 ^b
Triglyceride (mmol/L)	1.57±0.12	2.85±0.42 ^b	1.63±0.08 ^a
Atherogenic index ²	1.95±0.28 ^a	8.44±0.94 ^c	2.68±0.50 ^b
Liver			
Cholesterol (mmol/g)	0.16±0.01 ^a	0.28±0.06 ^b	0.20±0.03 ^a
Triglyceride	0.12±0.02 ^a	0.23±0.02 ^b	0.14±0.02 ^a

^{1,a,b,c}Means in the same row not sharing a common superscript are significantly different between groups ($p<0.05$).

²Atherogenic index: total cholesterol-HDL cholesterol/HDL cholesterol.

Source: From Cho et al., *Clin. Chim. Acta*, 317:109–117, 2002. With permission.

Hu and Kitts (2003) demonstrated, for the first time, the antioxidant and cytotoxic properties of dandelion-flower fractions. The two fractions, a water extract (WF) and an ethyl acetate (EAF) extract, both had significant ($p<0.05$) free-radical-scavenging activity for DPPH radical. EAF was a stronger scavenger than WF, although both had considerably less activity than TROLOX. Both fractions significantly ($p<0.05$) reduced the viability of a human colon colorectal adenocarcinoma cell line (Caco-2), with WF exhibiting greater toxicity. The most abundant bioactive compound identified in both fractions was the flavone luteolin-7-glucoside. It was considered to be the primary antioxidant present in dandelion flowers responsible for the protective effects observed. In order to establish dandelions as a potential source of natural antioxidants and bioactives, further research using *in vivo* models is required.

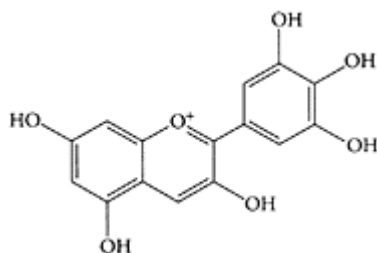
Trojanova et al. (2004) showed an infusion prepared from dandelion root with boiling water enhanced the growth of bifidobacteria species isolated from fermented milk products and infant feces. They attributed this prebiotic effect to the high quantity of nondigestible oligofructans present in dandelion roots.

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Delphinidin

Delphinidin is an aglycone (-glycosides) of one of the most abundant anthocyanins found in plant food sources. In addition to eliciting an endothelium-dependent relaxant



Delphinidin. (From Favot et al., *Cardiovasc. Res.*, 59:478–487, 2003. With permission.)

effect, it has been shown to inhibit the growth of human tumor-cell lines (Andriambeloson et al., 1998; Martin et al., 2002). Martin and coworkers (2003) showed delphinidin inhibited serum and vascular endothelium growth factor (VEGF), which normally induces proliferation of bovine aortic epithelial cells. The antiproliferation mechanism appeared to involve activation of ERK-1/2 pathway with overexpression of nitric-oxide synthase, shown previously to protect bovine aortic epithelial cells from apoptosis (Martin et al., 2001). This property of delphinidin should be important in atherosclerosis, as proliferation is crucial for the development and stability of atherosclerotic plaque. Using chicken embryos and human umbilicalvein endothelial cells (HUVECs), Favot et al. (2003) showed inhibition of angiogenesis by delphinidin affected two major steps, endothelial-cell migration and proliferation. At a minimal concentration of 10 $\mu\text{g/mL}$, delphinidin inhibited basal, as well as VEGF stimulation, of proliferation of HUVECs by 22 ± 3.9 percent and 21 ± 5.4 percent, respectively (Figure D.31). Inhibition of proliferation by delphinidin was correlated with blocking the cell cycle G0/G1 phase by reversing the VEGF-induced decrease of cyclin-dependent kinase inhibitor p27kip1 and VEGF-induced increase of cyclin D1 and cyclin A. Since a major step in angiogenesis is proliferation, which facilitates tumor growth, delphinidin should be a useful cancer chemopreventive agent.

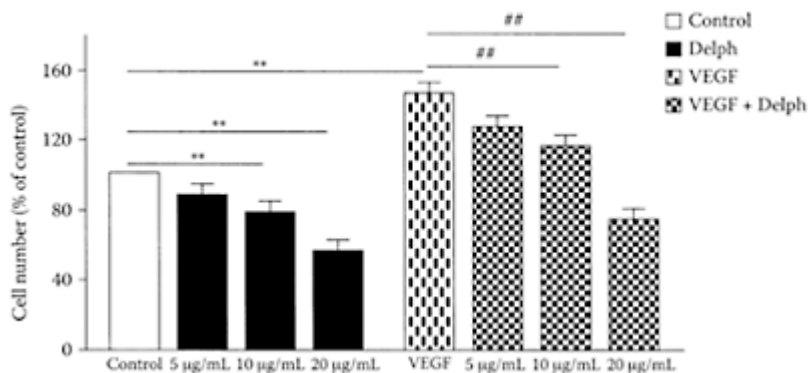


FIGURE D.31 Effect of delphinidin on basal- and VEGF-stimulated

proliferation of HUVECs incubated for 72 h with or without 5, 10, and 20 µg/mL delphinidin without or with 10 ng/mL VEGF. Data represent four experiments. ** $p < 0.01$ versus control cells, ## $p < 0.01$ versus VEGF-treated cells. (From Favot et al., *Cardiovasc. Res.*, 59:478–487, 2003. With permission.)

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Desert plant (*Retama raetum*)

Maghrani and coworkers (2003) show an aqueous extract from the desert plant, *Retama raetam*, significantly reduced the blood glucose in normal rats 6 hours after a single dose and two weeks after a second dose was administered. This hypoglycemic effect was found to be more pronounced in streptozotocin-induced diabetic rats. No effect was observed on plasma insulin levels, suggesting the mechanism was extra-pancreatic.

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Devil's claw

Devil's claw (*Harpagophytum procumbens*), a tuber with large, hooked, clawlike fruit, is used medicinally in Africa and Germany. Chrubasik et al. (1996) found it was effective for treating acute low-back pain. Subsequent reports demonstrated the ability of Devil's claw to improve rheumatic disorders (ESCOP, 1996; Wegener, 1998). Laudahn and Walper (2001) evaluated the clinical effectiveness and tolerance of an extract from Devil's claw in 117 patients suffering from nonradicular back pain over a six-month period. A film-coated tablet containing 480 mg *Harpagophytum* extract LI 174 was taken twice a day over the eight-week treatment period. A significant reduction in both the Arhus back-pain index and the multidimensional pain scale was recorded during over the treatment period. A significant increase in the mobility of the spinal column was observed, as measured by a significant reduction ($p, 0.001$) in the average finger-floor distance. This dropped from the initial 15.1 cm to 10.2 cm at the conclusion of the treatment and indicates a reduction in pain (Figure D.32).

This study reported that an alleviation of pain was experienced by 73.5 percent of all patients in this study to moderate to very good. The *Harpagophytum* extract was slow acting and could provide alternate treatment for those patients with known sensitivity to NSAIDs. The

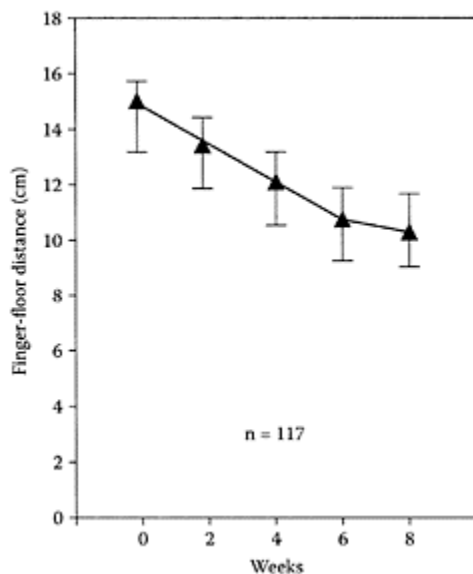
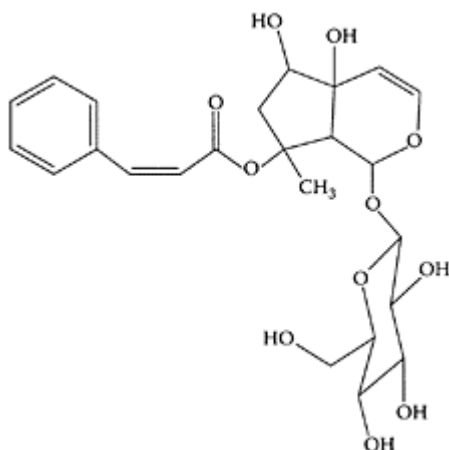


FIGURE D.32 Change in the average finger-floor distance (95 percent confidence interval, $p, 0.01$). (From Laudahn and Walper, *Phytother. Res.*, 15:621–624, 2001.)

mode of action appears to be anti-inflammatory and analgesic and may reflect the irioid glycosides present in the extract, particularly the main one, harpagoside. These studies suggest that Devil's claw may have considerable potential for the treatment of chronic back pain.



Harpagoside. (From Gunther and Schmidt, *J. Pharm. Biomed. Anal.*, 37:817–821, 2005. With permission.)

The anti-inflammatory properties of Devil's claw root extracts were demonstrated for the first time by Kaszkin and coworkers (2004) who showed two extracts high in harpagoside (8.9 percent and 27 percent) both attenuated IL-1 β -stimulated nitric-oxide (NO) formation in rat mesangial cells by inhibition of iNOSmRNA expression due to inhibition of NF- κ B activation. This inhibitory effect was not observed in extracts low in harpagoside so that its presence at high levels is required for the anti-inflammatory properties of Devil's claw. However, other unidentified constituents, in addition to harpagoside, also appeared to be involved.

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Diacylglycerol (DAG)

The introduction of diacylglycerol (DAG) oil, an edible oil enriched in DAG (80 percent), has unique health benefits. Studies focused on the nutritional properties of 1,3- and 1,2 (or 2,3)-DAG, which account for around 10 percent of various dietary oils. Particular interest in DAG was related to its ability to significantly lower serum triacylglycerols in rats fed a diet composed mainly of 1,3-DAG compared to triacylglycerols (TAG). In addition, Nagao et al. (2000) associated dietary DAG with a decrease in body weight and visceral-fat mass. Murase and coworkers (2001) examined

the effect of DAG on obesity, hyperinsulinemia, and hyperleptinemia in obese and diabetes-prone C57/6J mice. They found DAG suppressed body fat compared to TAG, even though they had similar fatty acids. The reduction in body fat, a recognized risk for diabetes and coronary heart disease, suggested a possible role for DAG in the management of obesity. Further work by Murase et al. (2002) on the long-term effects of dietary DAG on obesity in C57BL/6J rats showed marked changes in β -oxidation and related gene expression in the

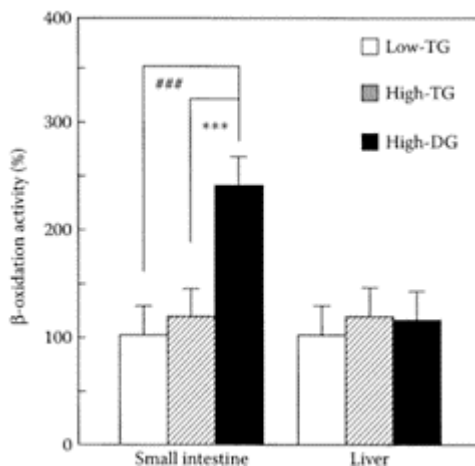


FIGURE D.33 β -Oxidation activity in the small intestine and livers of rats fed respective (TG, triacylglycerol; DG, diacylglycerol) diets for 10 days, as measured by palmitic-acid oxidation activities. Values expressed as means \pm SD. *** p <0.001 (From Murase et al., *J. Lipid Res.*, 43:1312–1319, 2002. With permission.)

small intestine (Figure D.33). Since the energy value per weight and digestibility for DAG and TAG were similar, the reduced body-fat accumulation effect by DAG had to involve another mechanism. DAG was shown to up-regulate mRNA levels in fatty-acid transport (fatty-acid transporter and liver fatty-acid-binding protein), β -oxidation (acetyl CoA oxidase and medium-chain acetyl CoA dehydrogenase), and thermogenesis (uncoupling protein) in the intestine. The potent stimulation of intestinal lipid metabolism by 1,3-DAG on overweight and obese men and women was shown by Maki et al. (2002) to reduce mean body weight by 3.6 percent compared to 2.5 percent for the TAG group. The weight loss and body-fat reduction promoted by the diet containing the DAG oil could be a useful addition to diet therapy for obesity. Kamphuis et al. (2003) showed the benefits associated with replacing modest amounts of TAG with DAG were decreased

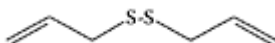
respiratory quotients and higher fat oxidation. In addition, several measures of appetite were significantly lower with DAG treatment, confirming its potential in diet therapy for obesity. Kasamatsu et al. (2005) recently reported that a diet incorporating DAG oil was safe with no evidence of any genotoxic effects.

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Diallyl disulfide

Diallyl disulfide (DADS) is formed during the eating of garlic or as a major component of cooked garlic. It is an oil-soluble sulfur compound accounting for 60 percent of garlic oil, which inhibits the proliferation of human colon-, lung-, and skin-cancer cells in culture (Sundaram and Milner, 1996a).



Diallyl disulfide. (Adapted from Tapiero et al., *Biomed. Pharmacother.*, 58:183–193, 2004.)

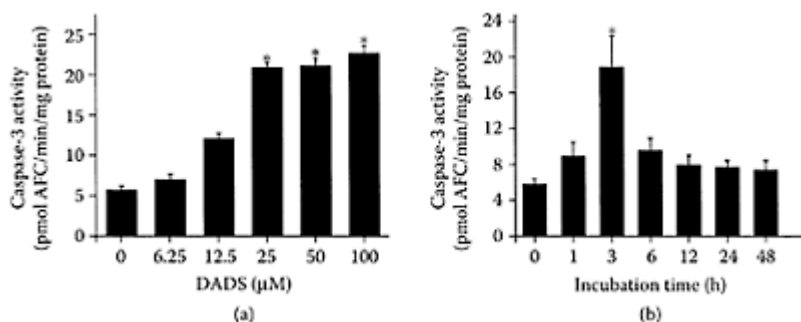


FIGURE D.34 DAD-induced apoptosis through activation of caspase-3 by treating HL-60 cells (5×10^6) with either (a) a range of concentrations (0–100 μM) of DAD for 3 h, or (b) 25 μM DAD for a period of 1, 3, 16, 24, and 48 h. Values represent means \pm SEMS of six separate experiments. Key: (*) $p < 0.05$ when compared with control by one-way ANOVA using Turkey's multicomparison procedures. (From Kwon et al., *Biochem. Pharmacol.*, 63:41–47, 2002. With permission.)

Sundaram and Milner (1996b) proposed that DADS induced apoptosis of human colontumor cells by enhancing the intracellular calcium concentration. Apoptosis, programmed cell death, can be initiated by oxidative stress through the production of reactive-oxygen species (ROS). These oxygen species then activate a family of cysteine proteases, caspases, involved in cell-death induction. Using human leukemia HL-60 cells, Kwon and coworkers (2002) examined the mechanism used by DADS to induce apoptosis. They provided evidence that incubating HL-60 cells with increasing levels of DADS stimulated the production of reactive-oxygen intermediates, with the subsequent activation of caspase-3 leading to the onset of apoptosis (Figure D.34).

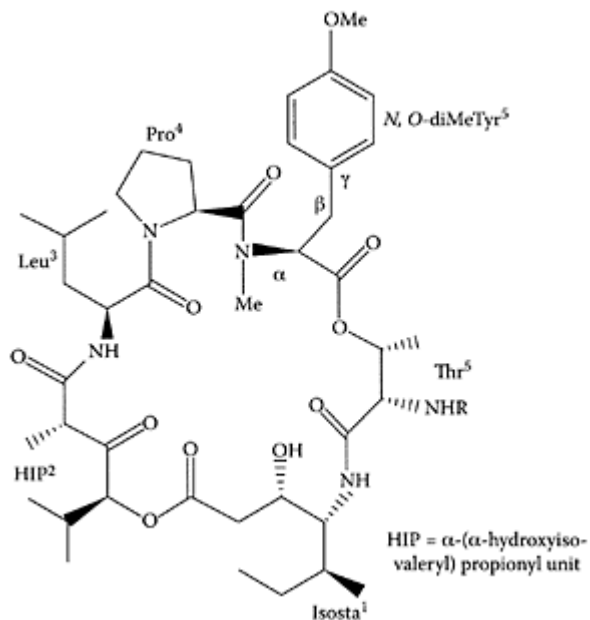
DADS was also found to exert a chemoprotective effect against benzo[*a*]pyrene (BP)-induced forestomach carcinogenesis in mice, which correlated with the induction of the expression of Pi class glutathione (GSH) transferase *mGSTP1-1*. Further work by Rose and coworkers (2002) showed the ally group in DADS was critical for its induction of *mGSTP1*, although the oligosulfide chain was equally important.

Oncogenes are very important in the transformation of normal cells into tumors. For example, oncogenes, such as *H-ras*, play a role in development and maintenance of solid tumors so that targeting and inhibiting these oncogenes could be an effective way

of inhibiting tumors. Using implanted experimental brain C6 glioma cells, Perkins et al. (2003) showed that expression of H-*ras* was significantly ($p < 0.05$) reduced in the brain-tumor tissue of rats treated with DADS prior to implantation.

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Didemnin B. (From Pfizenmayer et al., *Bioorg. Med. Chem. Lett.*, 8:3653–3656, 1998. With permission.)

Didemnin B

Didemnin B, a natural marine product, was first isolated from the Caribbean tunicate (sea squirt) (Reinhart et al., 1981). It is a cyclic depsipeptide that exhibits both antiviral and antitumor properties (Reinhart et al., 1981, 1983). Didemnin B was shown to induce apoptosis in human promycloid HL-60 cells at an optimum concentration of 1 μM (Grubb et al., 1995). Johnson and coworkers (1996) showed that didemnin B induced apoptosis via tyrosinase phosphorylation as it was inhibited by the addition of protein tyrosinase kinase inhibitors. Subsequent work by Beidler et al. (1999) showed induction of apoptosis in human breast-carcinoma cell MCF7 by didemnin involved activation of caspases. Apoptosis was only observed in the presence of 100 nM didemnin or higher, while inhibition of protein synthesis occurred at much lower levels with an IC_{50} of 12 nM. These researchers suggested the need for the development of didemnin B analogs that minimally affect protein synthesis while specifically targeting apoptosis of cancer cells.

Didemnin was shown to have promising preclinical antitumor activity at low concentrations (Crampton et al., 1984). A phase II study on didemnin B on advanced malignant melanoma by Hochster et al. (1999) showed some clinical activity, which needed further exploration. Other clinical trials on patients with recurrent or refractory anaplastic astrocytoma, Glioblastoma multiforme, or central nervous-system tumors, however, proved unsuccessful (Mittelman et al., 1999; Taylor et al., 1999). Aplidin[®], a compound similar to didemnin B with oxidation of the hydroxylic group of the side chain to ketone, was shown to have a lower toxic effect and better therapeutic indexes than didemnin B. Successful phase I studies with Aplidin[®] has led to a phase II trial for studying its pharmacokinetics.

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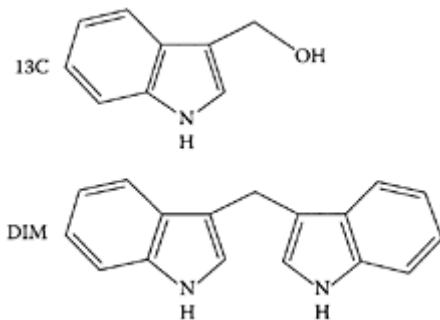
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3,3'-Diindolymethane (DIM)

3,3'-Diindolyl-methane (DIM) is produced by the autolytic breakdown of the glucosinolate, glucobrassicin. This glucosinolate is found in members of the *Brassica* genus, particularly broccoli, Brussels sprouts, cabbage, and kale. The enzyme involved,



13C (Indole-3-carbinol) and DIM (3,3"-Diindolyl-methane). (From Hong et al., *Biochem. Pharmacol.*, 63:1085–1087, 2002. With permission.)

myrosinase, hydrolyzes glucobrassicin to indole3-carbinol (13C) then condenses rapidly to form DIM. The 13C is a known inhibitor of breast cancer, with several *in vivo* and *in vitro* test studies showing it blocks the cell cycle (Sharma et al., 1994; Cover et al., 1998; Rahman et al., 2000). DIM also shows promise as an anticancer agent. Several studies found DIM inhibited DMBA-induced tumor growth in rodents by as much as 95 percent (Chen et al., 1998). Hong and coworkers (2002) examined the antiproliferative properties of DIM in human cancer cells. DIM was found to inhibit proliferation of estrogen-dependent and estrogen-independent human breast-cancer cells, inducing apoptosis by

decreasing cellular Bcl-2 levels and increasing Bax levels and the Bax/Bcl-2 ratio. The Bcl2-related family of proteins is involved in the final stage of apoptosis, or programmed cell death. This mechanism appeared identical to that reported previously for 13C, the precursor of DIM, which also induced apoptosis in human breast-cancer cells by regulating the Bcl-2 family (Rahman et al., 2000).

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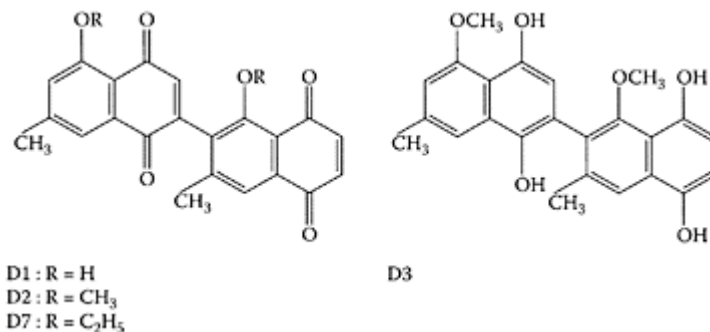
Dill oil

The essential oil of dill (*Anethum graveolens* L.) was reported to inhibit a broad range of microorganisms (Deans and Ritchie, 1987; Nakatani, 1994). Delaquis et al. (2002) examined the antimicrobial activity of a number of spices, including dill. While dill oil exhibited the lowest activity against the test organisms, distilled-oil fractions, containing higher concentrations of active components, were more effective. The main active components responsible were D-limonene and carvone, which accounted for 97.5 percent of those identified by gas chromatography. While D-limonene inhibited both Gram-negative and Gram-positive bacteria present in the pure extract, the dill oil itself had little effect on Gram-negative bacteria.

Lazutka and coworkers (2001) studied the genotoxicity of a number of essential oils, including dill oil. Dill was reported to be the most clastogenic, with the seed oil slightly greater than oil from dill herbs. The growing market for essential oils, such as dill, suggests the need to identify the genotoxic components so they can be reduced or removed by breeding.

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Structures of diospyrins D1, D2, D3, and D7 (From Chakrabarty et al., *Cancer Lett.*, 188:85–93, 2002. With permission.)

Diospyrin

Diospyrin, a bisnaphthoquinonoid isolated from the bark of *Diospyros montana* Roxb. in India, is a dimer of 7-methyljuglone linked together via C-2 to C-6 (Sidhu and Pardhasaradhi, 1967, 1976a,b). It was shown to inhibit Ehrlich ascites carcinoma in mice (Hazra and Banerjee, 1994). Norhanom and Hazra (1997) found diospyrin and its synthetic derivatives inhibited Epstein-Barr virus early antigen expression in Raji cells exposed to the carcinogen 12-*O*-tetradecanoylphorbol-13-acetate.

Adeniyi et al. (2000) later reported dimeric naphthoquinones, diospyrin and isodiospyrin, both exhibited antibacterial activity. Chakrabarty et al. (2002) examined possible anticancer properties of diospyrin (D1) and several derivatives, including diethyl ether diospyrin (D7). Using four human cancer lines (HL-60, K-562, MCF-7, and HeLa), the diethyl ether derivative was the most cytotoxic, while diospyrin the least (Figure D.35). Diethyl ether diospyrin appeared to induce apoptosis through activation of caspase-3 and caspase-8. While diospyrin induced apoptosis in human cancer-cell lines, diethyl ether diospyrin was a far more potent antitumor agent. The possibility of

developing new diospyrin derivatives with stronger anticancer properties as chemopreventive agents requires further study.

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Docosahexaenoic acid (DHA)

Docosahexaenoic acid (DHA, C₂₂:6 ω -3) is consumed primarily in fish oils. Epidemiological studies suggested that the levels of DHA in the blood were inversely associated with risk factors for cardiovascular disease. A study by Conquer and Holub (1998) showed that DHA supplementation in humans increased serum DHA as nonesterified fatty acid at levels that were potentially antithrombotic. Liu and coworkers (2001) found a significant increase in plasma omega3 fatty acids and in HDL-cholesterol in 36 hyperlipidemic patients fed bread containing fish oil. Since omega-3 fatty acids appear to inhibit the proliferation of breast-cancer cells, Chen and Auburn (1999) examined the effect of DHA on the growth of human papillomavirus immortalized keratinocytes. DHA was found to inhibit the growth of these cells and was dose dependent. Park and coworkers (2000) reported that fish oil had a protective effect against cardiovascular disease by inhibiting hepatic HMG CoA reductase activity and increasing hepatic microsomal fluidity, leading to a reduction in plasma lipids.

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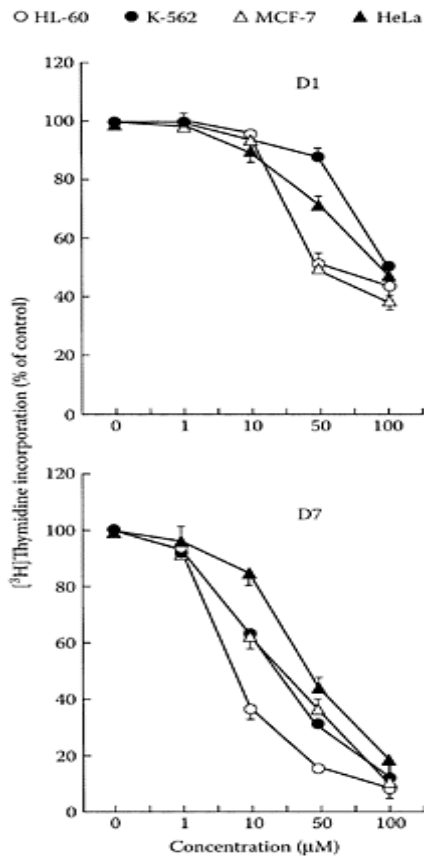


FIGURE D.35 Cytotoxicity on tumor cells induced by exposure for 48 h to different concentrations of diospyrin (D1) and diospyrin diethyl ether (D7) as assessed by MTT reduction. (From Chakrabarty et al., *Cancer Lett.*, 188:85–93, 2002. With permission.)

E

Echinacea (*Echinacea purpurea*)

Echinacea (purple coneflower), a perennial, flowering plant indigenous to North America, is used to treat such conditions as bacterial/viral infections, cancer, seizures, and AIDS (O'Hara et al., 1998). However, evidence supporting its use as a therapeutic agent remains controversial. It is a popular herbal product in Europe and North America, where it is used to prevent upper-respiratory-tract infections. Variable results have been reported regarding the efficacy of *Echinacea* due, in large part, to the lack of standards defining the active ingredients. The suggested bioactive constituents of *Echinacea* include lipophyllic alkylamides polar caffeic acid derivatives, such as cichoric acid, glycoproteins, and polysaccharides (Bauer and Wagner, 1991). Goel and coworkers (2002) designed a study to examine the dose-related effects of *Echinacea* extracts with different levels of bioactive components on immunomodulation in rats. Their results indicated that extracts with optimal concentrations of cichoric acid, alkylamides, and polysaccharides were potentially effective in stimulating a nonspecific immune response, *in vivo*, in rats.

Gan et al. (2003) examined the mechanism of immunomodulation by *Echinacea* by studying its effect on natural-killer (NK) cells present in human peripheral blood mononuclear cells (PMBC). NK cells defend against human viral infections by producing cytokinins IFN- γ , TNF- α , and GM-CSF. *Echinacea* appeared to be a potent activator of NK cytotoxicity, which explains, in part, its antiviral efficacy observed *in vivo*.

Carlo et al. (2003) compared the ability of *Echinacea* and St. John's Wort to modulate apoptosis in mice. Both exhibited significant, doserelated protection against apoptosis. For example, treatment of 30 mg/kg of *Echinacea* or St. John's Wort per day per mouse reduced apoptosis by 33 percent and 55 percent, respectively

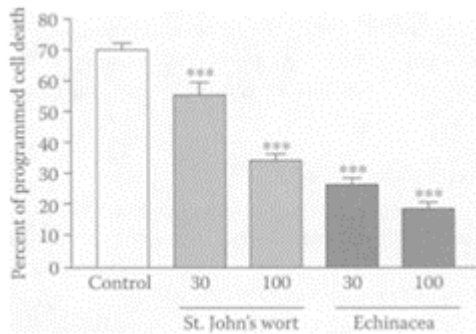


FIGURE E.36 Effect of St. John's Wort and *Echinacea* (30–100 mg/kg per day) on spontaneous apoptosis after 18 h *in vitro* cultivation. Values are means of at least seven determinations \pm SEM. *** p <0.001 versus control. (From Carlo et al., *Pharmacol. Res.*, 48:273–277, 2003. With permission.)

(Figure E.36). This reduction in apoptosis was accompanied by a corresponding decrease in Fas-Ag expression and an increase in Bcl-2 expression.

Echinacea products were used as adjuvants to reduce the side effects associated with cancer chemotherapy and radiotherapy (Bendel et al., 1988, 1989). The bioactive components involved are thought to be polysaccharide fractions containing neutral fucogalactoxyloglucans and arabino-galactans isolated from *Echinacea purpurea* cell cultures. Promising clinical and immunological effects were reported in patients with HIV-infection melanoma and leukemia who were injected with these polysaccharides (Emmendoerfer et al., 1999). A pilot study conducted in Germany by Melchart et al. (2002) showed injections of 2 mg of *Echinacea* polysaccharides in patients suffering from advanced gastric cancer slightly decreased leukopenia. The lack of a placebocontrolled group limited the outcome of this study, while production of adequate amounts of active and standardized *Echinacea purpurea* polysaccharide preparations remains a serious problem to be solved before further clinical trials can be carried out.

A novel diactylenic amide isolated from *Echinacea*, *N*-(2-methylpropyl)-2-*E*-undecene-8,10-diynamide, was recently synthesized by Kraus and Bae (2003). Such compounds were previously reported to be active against *A. aegyptii* larvae and *H. zea* neonates (Sun et al., 2002).

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Eggs

The relatively high cholesterol content of eggs deflected from their nutritional quality and led to a decrease in per capita consumption. Reviewing the available epidemiological data, Kritchevsky and Kritchevsky (2000) found only a moderate increase in the risk of coronary heart disease was associated with cholesterol intake. However, when other dietary confounders were taken into consideration, no risk of cardiovascular disease was evident in nondiabetic men and women consuming one-plus eggs per day. A cross-sectional and population-based study by Song and Kerver (2000) showed no association between egg consumption and serum cholesterol. This was supported by other researchers, who found egg consumption did not increase the risk of cardiovascular disease (Hu et al., 1999). A meta-analysis by Weggemans et al. (2001) found dietary

cholesterol from eggs increased the ratio of dietary cholesterol to high-density lipoproteins in humans. Using a randomized, controlled, crossover trial with 49 healthy adults, Katz et al. (2005) found that ingestion of two eggs daily over the short term had no adverse effect on endothelial function or cholesterol levels.

Feeding hens diets enriched with fish oils, vegetables oils, or algal sources of docosahexaenoic acid (DHA) produced eggs high in omega-3 fatty acids, which are now sold in the supermarkets. Human subjects fed seven enriched eggs a week had significantly higher level of blood omega-3 fatty acids and HDL cholesterol (Farrell, 1998). Makrides et al. (2002) reported that feeding both breast-fed and formula-fed infants 6 to 12 months of age four omega-3-enriched egg yolks a week increased DHA, hemoglobin, and ferritin without affecting

TABLE E.24

Effects of Dietary Casein and Ovomucin in Serum and Liver Lipids and Fecal Steroid Excretion in Rats¹

	Diet Group	
	Casein	Ovomucin
Serum		
Total cholesterol (a)	2.83±0.21	1.96±0.07 ^a
HDL cholesterol (b)	0.53±0.04	0.66±0.06
LDL+VLDL cholesterol	2.30±0.22	1.30±0.08 ^a
Atherogenic index: (b)/(a)(mol/mol)	0.19±0.02	0.34±0.03 ^a
TG	0.38±0.04	0.37±0.03
Phospholipids	1.13±0.08	1.04±0.05
Liver		
Total lipids (mg/g liver)	142.8±4.41	124.0±2.47 ^a
Cholesterol (µmol/g liver)	70.8±2.4	66.9±3.2
TG (µmol/g liver)	26.8±2.9	24.8±2.1
Phospholipids µ/3d)	118.8±3.2	98.7±1.6
Feces		
Dry weight (g/3d)	2.42±0.06	2.56±0.10
Cholesterol (µmol/3d)	252.5±6.7	281.3±9.5 ^b
Bile acids (µmol/3d)	126.5±5.8	151.9±7.2 ^b

¹Mean±SEM of six rats. Significantly different from casein control at:

^a*p*<0.01; ^b*p*<0.05.

From Nagoaka et al., *Lipids*, 37:267–272, 2002. With permission.

cholesterol levels. A recent study showed the potential health benefits associated with feeding CLA-enriched eggs to rats (Cherian and Goeger, 2003).

Despite its much-maligned image, eggs have always been considered to be a functional food. For example, egg white, the cholesterol-free protein, contains a number of protein fractions, including ovalbumin, ovomucin, ovotransferin, and lysozyme. Several studies have shown egg white is hypocholesterolemic (Yamamoto et al., 1993; Asato et al., 1996). Nagaoka et al. (2002) demonstrated, for the first time, the superior hypocholesterolemic properties of ovomucin compared to casein. *In vitro* studies with Caco-2 cultured cells showed ovomucin had greater bile-acid-binding capacity, inhibiting cholesterol absorption. *In vivo* studies further demonstrated the hypocholesterolemic effect of ovomucin compared to casein (Table E.24). Rats fed ovomucin had significantly lower levels of serum cholesterol and tended to have higher levels of HDL cholesterol compared to casein. In addition, the atherogenic index [(b)/(a)], defined as the ratio of HDL cholesterol to serum total cholesterol, was significantly higher than in the casein-fed group. This study illustrates the health benefits derived from the egg-white protein, ovomucin.

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Eicosapentaenoic acid (EPA)

Eicosapentaenoic acid (EPA)(C20:5 ω -3) is an ω -3 polyunsaturated fatty acid found primarily in sea and freshwater fish (Eskin, 2002). The extremely slow conversion of α -linolenic acid (C18:3 ω -3) to EPA by the human body makes fish an important source of this fatty acid. Minami and coworkers (2002) showed supplementation with EPA lowered plasma lipids, hepatic triacylglycerol levels, and abdominal-fat deposits accumulation, as well as improved insulin resistance in type 2 Otsuka Long-Evans Tokushima Fatty (OLETF) diabetic model rats (Table E.25).

A significant ($p<0.001$) correlation was observed between glucose-infusion rates and relative-weight abdominal fat in these animals, suggesting that the effect of EPA on insulin sensitivity was related to decreased abdominal-fat accumulation. Long-term feeding of EPA could help to prevent insulin resistance in diabetes-prone rats by improving hypertriacylglycerolemia.

The ability of ω -3 polyunsaturated fatty acids to modulate tumor-cell growth was demonstrated for EPA by Chiu and Wan (1999). They showed EPA arrested cell-cycle progression at G0/G1 phase, inducing necrosis in human leukemic HL-60 and K-562 cells *in vitro*. EPA, however, only induced apoptosis in HL-60 cells by down-regulation of Bcl-2. Gillis and coworkers (2002) found EPA, alone or in combination with gamma-linolenic acid (GLA: 18:3 ω -6), reduced cell survival by inducing

TABLE E.25

Effect of Dietary Supplementation with EPA for 25 Weeks on Fasting Plasma Lipids of Diabetic Rats¹

	Control		EPA	
	Mean	SD	Mean	SD
Triacylglycerol (mmol/L)	1.75	0.28	0.88*	0.27
Cholesterol (mmol/L)	1.7	0.18	1.23*	0.16
Phospholipids (mmol/L)	2.08	0.32	1.50*	0.24
Free fatty acids (mmol/L)	0.8	0.15	0.75	0.17

¹Eight rats per group. Mean values were significantly different from the control, * $p<0.05$.

Source: Adapted from Minami et al., *Br. J. Nutr.*, 87:157–162, 2002.

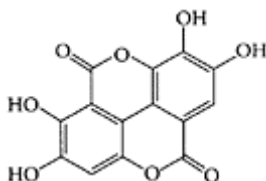
apoptosis and secondary necrosis in human promyelocytic HL-60 cells. Incubation of cells with 100 μ mol/L EPA reduced cell viability to 27 percent and increased apoptosis to 263 percent compared to the control.

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Ellagic acid

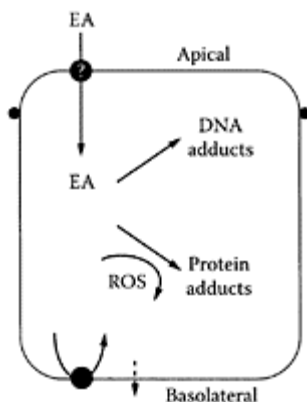
Ellagic acid, a complex planar molecule, has been attributed for the chemopreventive properties of berries, such as strawberries and raspberries. Siglin and coworkers (1995) reported that ellagic acid inhibited esophageal cancer in rats induced by *N*-nitrosomethylbenzy-lamine. Ellagic acid appeared to block the metabolic activation of the carcinogen, interfering



Ellagic acid. (Adapted from Mertens-Talcott and Percival, *Cancer Lett.*, 218:141–151, 2005)

with the binding of reactive carcinogen metabolites with DNA and by stimulating the detoxification enzymes (Teel et al., 1986; Ahn et al., 1996). Barch et al. (1996) demonstrated the anti-carcinogenic properties of ellagic acid, including inhibiting CYZP1A1-dependent activation of benzo[*a*]pyrene; binding and detoxifying the diolepoxide of benzo[*a*]pyrene; binding DNA and reducing the formation of O⁶-methylguanine by methylating carcinogenes; and inducing phase II detoxifying enzymes, glutathione *S*-transferase (GST) Ya, and NAD(P)H: quinone reductase. Structural examination of ellagic acid showed the 3- and 4-hydroxyl and the lactone groups were responsible for some of the different activities observed. Barch and coworkers (1995) previously showed in the rat that ellagic acid significantly increased total hepatic GST activity, hepatic GST-Ya activity and hepatic GST-YamRNA. The latter increased due to transcription induction of the GST-Ya gene by ellagic acid.

In order to be effective, ellagic acid must be available, but animal studies suggested only a fraction is orally bioavailable (Teel et al., 1988). Using a human intestinal-cell line Caco-2, Whitley et al. (2003) showed ellagic acid accumulated selectively in the epithelial cells of the areodigestive tract. Their results, illustrated in Scheme E.20, show ellagic acid (EA) enters the cell via the apical and is intercalated or bound to DNA. Another large portion is oxidized, possibly involving reactive-oxygen species (ROS), probably to quinines, where they bind to proteins. Losso and coworkers (2004) found that ellagic acid expressed a selective cytotoxicity and antiproliferative activity, and induced apoptosis in Caco-2, MCF-7m Hs 578T, and DU 145 cancer



SCHEME E.20 Proposed schematic model of EA disposition in epithelial Caco-2 cells. ROS, Reactiveoxygen species. ? denotes potential transporters. (From Whitley et al., *Biochem. Pharmacol.*, 66:907–915, 2003. With permission.)

cells, showing no toxicity toward normal lung fibroblast cells. Induction of apoptosis in cancer cells by ellagic acid involved a decrease in ATP production, essential to the viability of the cancer cells.

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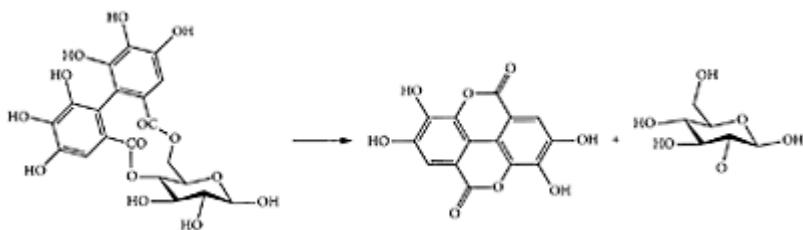
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Ellagitannins

Ellagic acid can also be complexed to form ellagitannins. These are water-soluble tannins, high-molecular-weight phenolic compounds capable of precipitating proteins and alkaloids (Santos-Beulga and Scalbert, 2000). They are structurally different from proanthocyanidins by being esters of hexahydroxydiphenic acid plus a polyol, glucose, or quinic acid (Scheme E.21). Acids and bases hydrolyze the ester bond, resulting in the formation of water-insoluble ellagic acid.

In Western diets, strawberries, raspberries, and blackberries are major sources of ellagitannins (Daniel et al., 1989). Ellagitannins are also in beverages produced from these fruit and loganberry (a hybrid of raspberry and blackberry) (Singleton et al., 1966), as well as in beer and tea (Nonaka et al., 1984). Ellagitannins appear to exert anticancer and antitumor properties. A study with transplantable tumors showed that number of ellagitannin oligomers (mainly dimers, but also a monomer, dimers, and tetramers) extended the life span of mice compared to the control (Yoshida et al., 1995). Castonguay and coworkers (1997) found raspberry ellagitannins containing sanguin H6 and lambertianin inhibited TPA-stimulated DNA synthesis, TPA-induced ornithine decarboxylase, and TPA-stimulated hydroperoxide production by 42 percent, 30 percent, and 30 percent, respectively. However, no full autopsy report was given by Castonguay et al. (1997) or a control group receiving just ellagitannins.



SCHEME E.21 Hydrolysis of ellagitannin to ellagic acid. (From Clifford and Scalbert, *J. Sci. Food Agric.*, 80:1118–1125, 2000. With permission.)

A number of reports have shown that some ellagitannins may be toxic to rodents and ruminants. Ellagitannin extracts were reported to inhibit a number of pathogenic bacteria (Scalbert, 1991; Silva et al., 1997). A recent review on ellagitannins by Clifford and Scalbert (2000), however, recommended that more work was needed to clarify their therapeutic benefits.

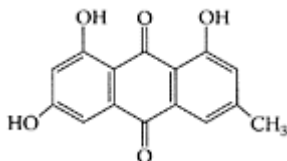
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Emodin

Emodin (1,3,8-trihydroxy-6-methy-lanthraquinone), a naturally occurring constituent of many Chinese herbs, is known for antibacterial, anticancer, diuretic, immunosuppressive, and vasorelaxant properties (Muller et al., 1996; Wang et al., 1998; Lee, 2001). Koyama

and coworkers (2002) showed emodin exhibited potent antitumor properties. Using a two-stage carcinogenesis test of mouse-skin tumors induced by topical application of 7,12-dimethyl-benz [*a*] -anthracene as an initiator and 12*O*-tetradecanoylphorbol-13-acetate as a promotor, emodin inhibited the two-stage carcinogenesis test very effectively. Emodin was first shown to induce apoptosis in human kidney fibroblasts from lupus nephritis patients (Liu et al., 2000). Since then, other studies have shown



Emodin. (From Koyama et al., *Cancer Lett.*, 182:135–139, 2002. With permission.)

apoptosis-inducing properties of emodin, including the structurally similar compound, aloe-emodin, on neuroectodermal cancer and lung-carcinoma cells (Lee et al., 2001; Pecere et al., 2000). Chen and coworkers (2002) showed emodin-induced apoptosis in human promyeloleukemic HL-60 cells via activation of the caspase-3 and not by its prooxidant activity. Srinivas et al. (2003) suggested the antiproliferative effects of emodin in human cervical cancer cells was mediated through the induction of apoptosis. They also found that the induction of apoptosis by emodin was mediated by activation of caspase via the mitochondrial pathway.

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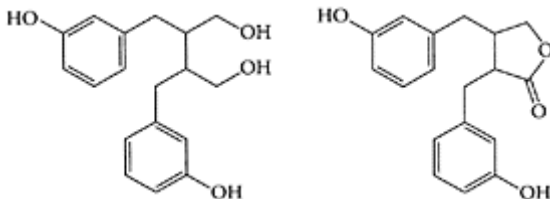
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Enterodiol and Enterolactone

Enterodiol [2,3-bis(3-hydroxybenzyl)butane-1,4-diol] and enterolactone [trans-2,3-bis (3-hydroxy-benzyl)- γ -butyrolactone] are lignan-type phytoestrogens produced by bacteria in the intestinal tract (Axelson et al., 1981, 1982) and from plant lignans matairesinol and seco-isolariciresinol (Borriello et al., 1985). These plant lignans are found in whole-grain cereals, seeds, nuts, legumes, and vegetables.

Enterodiol and enterolactone are both estrogens and exert protective effects by their ability to compete with estradiol for the type II estrogen receptor. Mousavi and Adlercreutz (1992) showed enterolactone at $>10\text{ }\mu\text{M}$ inhibited the growth of MCF-7 breast-cancer cells, while higher concentrations ($>50\text{ }\mu\text{M}$) were found by Wang and Kurtzer (1997) to inhibit DNA synthesis. Other protective effects include the induction of the sex hormone-binding globulin as well as their inhibition of a number of steroid-metabolizing enzymes, including aromatase, 5- α -reductase, 7 α -hydroxylase, and 17 β -hydroxysteroid dehydrogenase. Aromatase appeared to play some role in the development of breast cancer and was moderately inhibited by enterolactone compared to enterodiol, a weaker inhibitor (Adlercreutz et al., 1993; Wang et al., 1994; Makeda et al., 2000). These phytoestrogens were also shown by Sanghvi et al. (1984) to significantly inhibit cholesterol 7 α -hydroxylase (the rate-limiting enzyme for bile acids) *in vitro*, decreasing the formation of primary bile acids, thereby providing protection against colorectal cancer. The final, protective role of these phytoestrogens is due to their antioxidant properties.

During the menstrual cycle these phytoestrogens are excreted in large amounts, particularly during early pregnancy. Postmenopausal Japanese women who consumed large quantities of phytoestrogens in their diets were reported to have fewer complaints of hot flushes, night sweats, and other symptoms compared to women in other countries (Williams and Rutledge, 1998). Lignans, such as enterolactone, also appear to exert a chemoprotective effect against prostate cancer, as well coronary heart disease (Denmark-Wahnefried et al., 2001; Department of Health, 1994). An excellent review on enterodiol and enterolactone was published by Wang (2002).



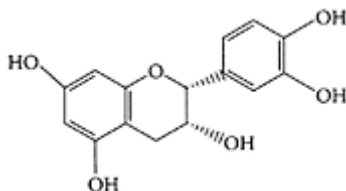
Enterodiol, Enterolactone. (Adapted from Penalvo et al., *Anal. Biochem.*, 332:384–393, 2004.)

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(–)-Epicatechin (EC)

(–)-Epicatechin is a dietary flavonol present in many fruits, red wine, green teas, and cocoa products. *In vivo* studies showed that only small amounts of epicatechin are absorbed and converted to various



Epicatechin. (Adapted from Geetha et al., *Mutat. Res.*, 556:65–74, 2004.)

metabolites, including glucuronides, methyl derivatives, and sulfates. More than 60 μM of epicatechin and its metabolites were reported in the plasma of rats, following a single, intragastric dose of 100 mg (Scalbert and Williamson, 2000). Epicatechin was also reported in human plasma, following consumption of chocolate (Wang et al., 2000). Together with one of its *in vivo* metabolites, 3'-O-methyl epicatechin, epicatechin appeared to protect against neuronal cell death induced by oxidative stress (Schroeter et al., 2001). El-Mohsen et al. (2002) identified the presence of both epicatechin glucuronide and 3'-methyl epicatechin glucuronide in rat-brain tissue, following oral ingestion of (–)-epicatechin.

During inflammatory processes, peroxynitrite is formed by the action of superoxide and nitrogen monoxide, triggering activation of cellular stress-responsive signaling pathways, some of which may result in cell death (Radi et al., 2000; Klotz et al., 2002). (–)-Epicatechin appears capable of protecting biomolecules from oxidation and nitration by peroxynitrite (Pannala et al., 1997; Haenen et al., 1997; Schroeder et al., 2000). Schroeder and coworkers (2003) demonstrated the importance of the amphiphilic properties of (–)-epicatechin in protecting against peroxynitrite-induced nitration in both hydrophilic and lipophilic cellular phases. The removal or loading of (–)-epicatechin by murine endothelial cells from plasma suggests that under physiological conditions, it may be present to protect against damage from peroxynitrite.

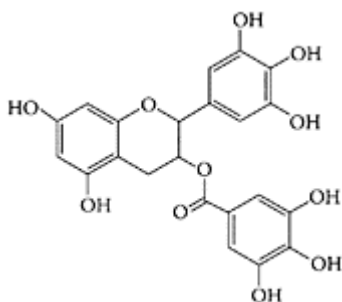
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Epigallocatechin gallate (EGCG)

see also Green tea Epicatechin-3-gallate (EGCG) is one of the major water-soluble components in green tea. The antimutagenic properties of EGCG were shown by Muto et al. (1999) to



Epigallocatechin gallate. (Adapted from Furukawa et al., *Biochem. Pharmacol.*, 66:1769–1778, 2003.)

reduce benzo[*a*]pyrene (B[*a*]P)-induced mutations in the *rpsL* gene in the lung of 7-week-old mice by 60 percent. Pretreatment with EGCG was also found by Katiyar et al. (2001) to protect human skin from multiple exposures to UV light by inhibiting the production of hydrogen peroxide and nitric oxide in both the epidermis and dermis, as well as inflammatory leukocytes, CD11b⁺ (a surface marker of monocytes/macrophages and neutrophils), the major producers of reactive-oxygen species. EGCG protected the antioxidant enzyme, glutathione peroxidase, as well as restored total glutathione levels reduced by UV-exposed skin. Ohishi and coworkers (2002) reported EGCG acted synergistically with Sulindac, a well-established cancer-preventive agent, against colon cancer. The combination of EGCG and Sulindac significantly ($p < 0.01$) reduced the number of aberrant crypt foci (ACF)/colon to 10 ± 3.2 in AOM-induced rat-colon carcinogenesis compared to 21.4 ± 3.4 and 19.5 ± 5.8 for Sulindac and EGCG treatments,

respectively. The synergistic effects of the combined treatment with Sulindak and EGCG enhanced apoptosis, suggesting EGCG could reduce the adverse side effects associated with such cancer-preventive agents as sulindak.

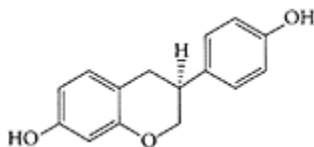
The antiatherosclerotic effects of EGCG were due to its inhibition of platelet function from inhibiting cytoplasmic calcium increase (Kang et al., 1999). Recent work by Lill and coworkers (2003) showed EGCG was the only active principle in green tea exerting plateletinhibitory effects. EGCG was found to interrupt other signaling-transduction pathways, such as phosphorylation of p38 mitogen-activated protein kinase (MAPK) and extracellular signalregulated kinase (ERK)-1/2. The presence and the location of the galloyl group appeared important for platelet aggregation. Catechin gallate (CG) and epicatechin gallate (ECG), with a galloyl group at the 3' position, both stimulated platelet aggregation, while catechins without a galloyl group (catechin [C], epicatechin [EC]) or with the group in the 2' position (epigallocatechin) were inactive.

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Equol

Equol (7-hydroxy-3-(4'-hydroxyphenyl)-chroman), an estrogenic metabolite of daidzein, is a potent antioxidant formed in the intestinal tract by bacteria (Axelson et al., 1982). The ability to form and excrete equol appears to be linked to the beneficial effects of isoflavone



Equol. (Adapted from Muthyala et al., *Bioorg. Med. Chem.*, 12:1559–1567, 2004.)

intake and its regulation of endogenous hormones (Duncan et al., 2000). Equol excretors, with a more favorable hormone profile, were found to have a significantly lower risk of breast cancer. The more potent antioxidant properties of equol made it a far more effective inhibitor of LDL oxidation compared to daidzein or genistein (Yamakoshi et al., 2000). Hwang et al. (2003) showed equol inhibited LDL oxidation in J744 macrophage cells by reducing superoxide production, in part, by inhibiting NADPH oxidase activity. The overall effect was to prevent the modification of LDL to an atherogenic particle.

In addition to being one of the most biologically active metabolites of daidzein, equol had a significantly longer half-life in the body (Kelly et al., 1995). Equol was reported to have greater antiproliferative (Verma and Goldin, 1998; Dubey et al., 1999) and estrogenic (Markiewicz et al., 1993) activities in nonprostatic cells. The low incidence of prostate cancer in Asians because of the high levels of soy in their diet suggests equol may have a protective role against prostate cancer. Examination of prostatic fluids showed equol levels were present at much higher levels in Asians compared to Caucasians (Morton et al., 1997). Hedlund and coworkers (2003) treated benign and malignant prostatic epithelial human cells with equol, daidzein, and genistein within concentration range found in prostatic fluids. Equol was found to be 10 times more potent than daidzein, inhibiting the growth of benign human prostatic epithelial cells by 37 percent and 80 percent in the presence of 10^{-6} and 10^{-5} M, respectively. It also exerted strong, antiproliferative effects against malignant cells at concentrations available in a normal soybean-containing diet.

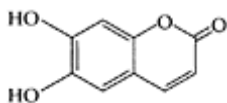
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Esculentin

Esculentin, a coumarin derivative present in many plants, including the Chinese herb *Artemisia scoparia*, has been used for centuries in China as folk medicine. It has multiple biological activities, including inhibiting xanthine oxidase, platelet aggregation, and chemically induced mammary and lung carcinogenesis by *N*-methyl-*N*-nitrosourea and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, respectively (Egan et al., 1990; Okada et al., 1995; Matsunaga et al., 1998; Hecht et al., 1999). In addition to inhibiting soybean lipoxygenase (Neichi et al., 1983), esculentin is an antioxi-



Esculentin. (Pan et al., *Biochem. Pharmacol.*, 65:1897–1905, 2003.
With permission.)

dant (Lin et al., 2000), as well as inhibits the growth of human cancer cells (Noguchi et al., 1995). The antitumor property of esculentin was reported by Chu et al. (2001), as it induced apoptosis in human leukemia cells HL-60. The induction of apoptosis by esculentin was associated with cytochrome c translocation and caspase activation. Further work by Wang et al. (2002) showed esculentin inhibited the growth of human leukemia HL-60 cells in a time- and

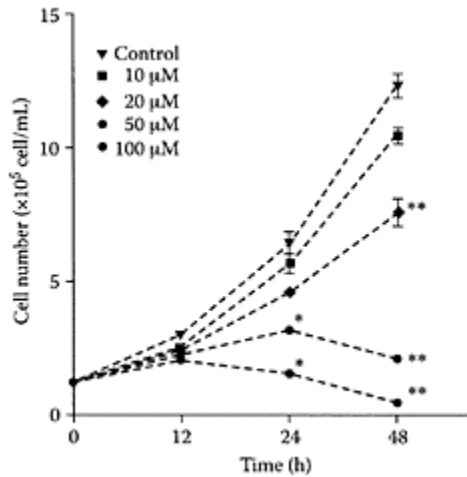


FIGURE E.37 Effect of esculetin on the growth of human leukemia HL-60 cells treated with different concentrations of esculetin for 12, 24, and 48 h. Cells were counted using the trypan blue-dye exclusion assay. Results are the mean±SD of three independent experiments, with levels of significance at * $p<0.05$; ** $p<0.01$ compared to a control group with DMSO (0.1 percent). (From Wang et al., *J. Cancer Lett.*, 188:163–168, 2002. With permission.)

dose-dependent manner (Figure E.37). A significant inhibition of growth was evident in the presence of 50 and 100 μM. The ability of esculetin to inhibit the growth of human leukemia HL-60 cells involved G1 phase cell-cycle arrest, as a result of inhibition of retinoblastoma protein (pRb) phosphorylation.

Vascular-proliferative disorders, such as atherosclerosis and restenosis, result from the proliferation of vascular smooth cells (VSMCs) induced by injury to the intima of the arteries. Recent studies by Pan et al. (2003) showed esculetin effectively inhibited VSMC proliferation and intima hyperplasia by blocking intima thickening in the artery of rats. Inhibition of cell proliferation by esculetin occurred via inhibition of an upstream effector of Ras and downstream events for three predominant signaling pathways, p42/44 MAPK activation, PI-3 activation, and early gene expression, as well as NK-κB and AP-1 activation. These results point to the potential therapeutic use of esculetin for treatment of restenosis following arterial injury.

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Ethanol

see also Alcohol Overall epidemiological evidence points to an association between alcohol consumption and increased risk of breast cancer (Smith-Warner et al., 1998). The association between alcohol consumption and circulating levels of steroid hormones, such as estradiol (Ginsberg, 1999), impaired immune systems, greater proliferation of mammary glands, and altered carcinogen metabolism (Singletary, 1997) are among the mechanisms proposed. Alcohol intake has also been linked to greater risks for breast tumors, depending on their hormone-receptor status. Singletary et al. (2003) showed increased cell proliferation, and cellular cAMP content only occurred when ethanol was added to human breast-cancer cell lines supplemented with estrogen receptors (ER+). Thus, the ability of ethanol to only stimulate proliferation of human breast-cancer cells

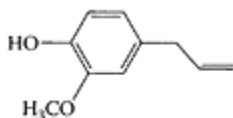
with specific hormonereceptor characteristics may explain the modest increase in breast-cancer risk observed in epidemiological studies.

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Eugenol

Eugenol (4-allyl-1-hydroxy-2-methoxybenzene), a naturally occurring alkenylbenzene, is found in cloves, as well as in cinnamon, basil, and nutmeg (Rompelberg et al., 1993).



Eugenol. (Yoo et al., *Cancer Lett.*, 225:41–52, 2005. With permission.)

While it is used mainly as a flavoring agent, it was shown to be an effective inducer of detoxifying phase II enzyme (Rompelberg et al., 1993; Newberne et al., 1999). Eugenol also behaves as a chain-breaking antioxidant and inhibits lipid peroxidation (Nagababu and Lakshmaiah, 1992). The antimutagenic properties of eugenol were confirmed in a number of different studies (Rompelberg et al., 1995, 1996 a, b, c). Abraham (2001) examined the antigenotoxic effects of *trans*-anethole and eugenol in male Swiss albino mice treated with genotoxins, cyclophosphamide (CPH), ethyl methane sulfonate (EMS), *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG), micronucleated polychromatic erythrocytes (Mn PCEs), procarbazine (PCB), polychromatic erythrocytes (PCEs), and urethane (URE). No antigenotoxic effects were observed when mice were administered eugenol and *trans*-anethole separately. However, pretreatment with both of these flavoring agents resulted in significant antigenotoxic effects against CPH, MNNG, and EMS. Dose-related antigenotoxic effects were also reported for both eugenol and *trans*-anethole against PCB and URE. A moderate, protective effect against these genotoxins was only observed in the combined presence of eugenol and *trans*-anethole.

The antiviral activity of eugenol was demonstrated by Benencia and Courreges (2000), who found it delayed the development of herpetic keratitis in the cornea of HSV-1 mice. *In vitro* studies showed eugenol inhibited the replication of the human herpesvirus and behaved synergistically with the drug acyclovir.

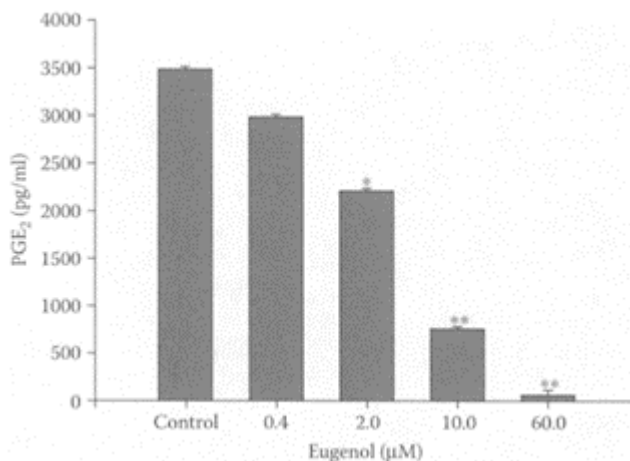
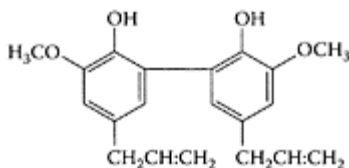


FIGURE E.38 Effects of eugenol on COX-2 enzyme activity in RAW264.7 cells stimulated with LPS (1 μg/mL) for 24 h and pretreated with eugenol for 30 min prior to adding exogenous arachidonic acid. After 15 min, the supernatant was removed and analyzed for PGE₂. Values significantly different from the control are shown by; *, $p < 0.05$, **, $p < 0.01$. (Kim et al., *Life Sci.*, 73:337–348, 2003. With permission.)

Kim et al. (2003) studied the effect of eugenol, isolated from clove (*Eugenia caryophyllata*), on COX-2 and gene expression of lipopolysaccharide (LPS)-activated mouse macrophages. Since COX-2 is implicated in inflammatory and carcinogenic processes, inhibition of this enzyme could help to prevent these processes. The direct inhibition of COX-2 by eugenol was demonstrated by its inhibition of PGE₂ formation in a dose-dependent manner in intact cells where the enzyme was induced by LPS and exogenous arachidonic acid as substrate (Figure E.38). Eugenol also inhibited the growth of human cancer cells by suppression of COX-2 gene expression, suggesting a possible role in cancer prevention.

An *ortho* dimer of eugenol, *bis-eugenol*, was shown by Murakami et al. (2003) to be a more potent antioxidant than eugenol and less cytotoxic. It inhibited lipopolysaccharide-stimulated activation of NF- κ B, a transcriptional factor regulating inflammatory responses and cytokine expression. These researchers suggested *bis-eugenol* could be used in preventing oral diseases, as inhibition of NF- κ B may prevent bacterium-stimulated alveolar bone resorption associated with adult periodontal diseases.



bis-Eugenol. (Murakami et al., *Biochem. Pharmacol.*, 66:1061–1066, 2003. With permission.)

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Evening primrose

Evening primrose (*Oenothera biennis* L.) is a biennial plant belonging to the family *Onagracea*, a common weed native to North America. The oil content of the seeds is in range 17–25 percent, of which 7–10 percent is gamma linolenic acid (GLA, C18:3 ω -6). There is a growing demand for evening primrose oil because of the clinical and pharmaceutical applications associated with GLA. Oral administration of evening primrose, attributed to GLA, was found to substantially inhibit the growth of implanted human tumors in rats. High doses of oral GLA in the form of evening primrose oil elicited a response that prolonged life, without side effects, of patients suffering from liver, breast, brain, and esophageal cancers (Horrobin, 1994). The British Department of Health licensed evening primrose oil for the treatment of breast pain and premenstrual disease because of the effectiveness of GLA in relieving these symptoms (Horrobin, 1992).

Diabetes impairs the conversion of linoleic acid to its ω 6-desaturated metabolites in humans, which is associated with renal, retinal, and neurological damage. In alcoholics, GLA appears to accelerate recovery of the liver, as well as reduce the severity of withdrawal symptoms. Other studies have shown GLA significantly reduced skin roughness in atopic eczema, as well as some clinical benefits on rheumatoid arthritis (Belch and Hill, 2000). Hamburger and coworkers (2002) recently found lipophilic radical scavengers in cold-pressed, nonraffinated evening primrose oil. Three esters exhibiting the most pronounced radical-scavenging activities and potent inhibitors of neutrophil elastase and cyclooxygenase 1 and 2 *in vitro* were 3-*O*-trans-caffeoyl derivatives of betulinic, morolic, and oleanolic acids. In addition to GLA, evening primrose also contains antioxidative phenolic compounds (Shahidi et al., 1997). Subsequent work by Amarowicz et al. (1999) found pronounced antioxidative activity in the ethanol extracts of evening primrose, as well as its hydrophilic and hydrophobic fractions.

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F

Farnesol

Farnesol, a nonsteroid isoprenoid intermediate formed from mevalonate, is found in orange-peel oil and lemon-grass oil. In mammalian cells, farnesol is metabolized to farnesal, farnesoic acid, and prenyldicarboxylic acids (Bostedor et al., 1997). Isoprenoids, such as farnesol, are involved in cell-signaling transduction, as its phosphorylated form, farnesyl



Farnesol. (Adapted from Rao et al., *Cancer Det. Prev.*, 26:419–425, 2002.)

pyrophosphate, is needed for protein prenylation (Gelb, 1997). Terpenoids, such as farnesol, with hydroxyl groups appear more active than terpene hydrocarbons by inhibiting MIA ZpaCa2 pancreatic-tumor cells (Burke et al., 1997). Farnesol was reported to inhibit the proliferation of some cell lines and induce apoptosis in a number of tumor-derived cell lines (Burke et al., 1997; Yasugi et al., 1994). Rioja et al. (2000) showed farnesol preferentially inhibited proliferation and induced apoptosis of leukemic cells without affecting normal, nontransformed cell lines.

Raner et al. (2002) observed that only farnesol, and not related isoprenoids, geranylgeraniol, geranylgeranyl pyrophosphate (GGPP), and farnesyl pyrophosphate (FPP), inhibited certain rabbit-liver microsomal cytochrome P450 enzymes (Table F.26). Since cytochrome P450 plays a prominent role in the metabolism of pharmaceuticals and activation of potential carcinogens, its inhibition has important health benefits. Studies on AOM-induced colon carcinogenesis in rats by Rao et al. (2002) noted the chemopreventive properties of farnesol as it inhibited the formation of preneoplastic lesions in rats fed a diet containing 1.5 percent farnesol. Farnesol significantly inhibited ACF formation by 34 percent, while reducing multiplicity by 44 percent.

TABLE F.26

Percent Inhibition of Different P450 Activities in Rabbit-Liver Microsomes and a Reconstituted P450_{2E1} System By Four Different Isoprenoids^{1,2}

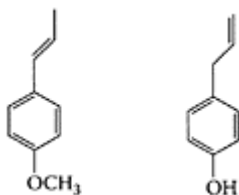
Activity	Farnesol	Geranylgeraniol	FPP	GGPP
In rabbit-liver microsomes				
p-Nitrophenol hydroxylation (30 μ M)	60 \pm 5		0 \pm 1	10 \pm 5
Diclofenac-4-hydroxylation (0.20 mM)	45 \pm 2		2 \pm 1	1 \pm 1
Caffeine-N-demethylation (2.0 mM)	35 \pm 2		0 \pm 1	0 \pm 1
In reconstituted P450 _{2e1} -3-27				
p-Nitrophenol hydroxylation (45 μ M)	43 \pm 3		2 \pm 2	3 \pm 1
¹ Concentration of each isoprenoid was 80 μ M.				
² Errors based on the average deviation from the mean for three or more trials.				
Source: From Raner et al., <i>Biochem. Biophys. Res. Commun.</i> , 293:1–6, 2002. With permission.				

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Fennel

Fennel (*Foeniculum vulgare* Mill.) is an aromatic herb grown in Europe and Asia. The essential oil from the seeds of fennel has been used in foods, cosmetics, and pharmaceuticals. The major constituent of fennel oil is (E)-anethole (80 percent), followed by methyl chavicol (10 percent) and fenchone (7.5 percent) (Brand, 1993). Minor constituents include γ -pinene, limonene, β -pinene, α -myrcene, and



Arethole chavical. (Adapted from Gross et al., *Plant Sci.*, 163:1047–1053, 2002.)

para-cymene (Brand, 1993; Toth, 1967; Trenkle, 1972). The essential oil of *Foeniculum vulgare* was found by Ozbeck et al. (2003) to exert a potent hepatoprotective effect against carbon tetrachloride (CCl₄)-induced liver damage in rats.

Fennel seeds have been reported to promote menstruation, alleviate female climacteric, as well as increase libido (Albert-Puelo, 1980). Because of its antispasmodic effects, it has been used to treat some respiratory disorders (Reynolds, 1982). In folk medicine, fennel has been used to treat a number of gynecological complaints, such as dysmenorrhea, a condition of severe pain during menstruation. One of the major reasons for primary dysmenorrhea is increased ectopic uterine motility. Ostad et al. (2001) showed fennel essential oil significantly reduced the intensity of oxytocin- and PGE₂-induced uterine contractions obtained from virgin Wistar rats. Subsequent work by Namavar Jahromi et al. (2003) compared the effectiveness of sweet fennel (*Foeniculum vulgare* var. *duice*) and mefenamic acid in the treatment of primary dysmenorrhea in 70 women 15–24 years old, suffering from this problem. The results in Table F.27 show mefenamic acid was more effective in reducing pain intensity on the second and third days of menstruation, but there were no significant differences on any of the other days. This study corroborates earlier studies confirming the effectiveness of fennel extract in treating primary dysmenorrhea.

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TABLE F.27

Mean Intensity of Pain Reported By the Subjects and *P*-Values Measured Using the Paired *T*-Test for the Treated Cycles

Days	ControlCycles	Mefanamic-Acid-TreatedCycles	Fennel-Extract-TreatedCycles	<i>P</i> -Values
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Day 1	9.9667	9.4167	9.5833	0.382
Day 2	7.0667	4.4167	5.4167	0.024
Day 3	4.2333	2.1667	3.125	0.052
Day 4	1.8667	0.5833	0.9583	0.384
Day 5	0.2759	0.167	0.1167	0.184

Source: From Namavar Jahromi et al., *Inter. J. Gynecol. Obstr.*, 80:153–157, 2003. With permission.

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Fenugreek

Fenugreek (*Trigonella foenum graecum*) seeds, widely used as a condiment, have also proved beneficial in India for the treatment of gastric disorders (Puri, 1968). They were shown to be beneficial in treating diabetics and hypercholesterolemic patients (Sharma et al., 1996). Pandian and coworkers (2002) reported that several fenugreek fractions were effective in treating an HCl-ethanol-induced gastric ulcer in rats compared to one of the commonly prescribed drugs, omeprazole. Fenugreek seeds were extracted with water and centrifuged with the supernatant used as the aqueous extract. A gel fraction was also prepared, following the procedure of Madar and Shomer (1990), which represented the polysaccharides of the seed coat. The severity of the ulcers was reduced markedly, following pretreatment of the rats with the fenugreek fractions prior to HCl-ethanol treatment. Maximum inhibition was observed with doses of 3 mL of the aqueous fractions and 700 mg of the gel fraction, with the results summarized in Table F.28. The fenugreek fraction proved to be as effective as omeprazole against the ulcerogenic effects of ethanol. Lipid peroxidation, as measured by TBARS, was found to be significantly

lower in the pretreated rats compared to ethanol-treated rats, suggesting antioxidant activity in the fenugreek extracts, due possibly to the presence of flavonoids.

Al-Habouri and Raman (1998) reviewed the literature related to antidiabetic and hypocholesterolemic effects of fenugreek. While the antidiabetic effects were attributed to the gum fiber, the hypolipidemic effects were due to the saponins and sapogenins confined fiber. The lack of toxicity associated with fenugreek makes it excellent for management of diabetes and hypercholesterolemia. Recent work by BinHafeez et al. (2003) showed fenugreek also had appreciable immunostimulatory activity.

Concern was raised regarding the potential of fenugreek to react with medications, such as warfarin (Lambert and Cormier, 2001; Heck et al., 2000). In addition, fenugreek may also potentiate antihypertensive and antidiabetic medication, as well as increase the risk of bleeding in women taking nonsteroidal antiinflammatories, such as aspirin (Abebe, 2002).

TABLE F.28

Effect of Pretreatment with Fenugreek-Aqueous Extract (3 mL/rat), Gel Fraction (700 mg/rat), and Omeprazole (10 mg/rat) on the Volume of Gastric Secretion, Total Acidity, Pepsin Activity, and Protein Content in Ethanol-Treated Rats

	Normal	HCl-EtOH	Fenugreek-Aqueous Extract+HCl-EtOH	Fenugreek Gel +HCl-EtOH	Omeprazole +HCl-EtOH
Volume	3.38±0.16	5.73±1.9*	4.00±1.77**	4.8±0.23**	4.2±0.20**
Total acidity ¹	121.0±10	74.4±15.5*	60.43±6.8**	68.5±4.8**	76.6±1.8
Pepsin activity ²	1.56±0.2	2.56±0.6*	1.64±0.04**	1.65±0.2**	1.64±0.03**
Protein (mg/mL)	0.96±0.2	3.78±0.05*	2.35±0.07**	2.38±0.7**	1.83±0.05**
Ulcer score	0	25.8±0.75	11.16±0.75	9.14 ± 1.27**	17.6±1.5**

¹mEq/3 h.

²μg tyrosine liberated/mg protein/h. Values are means±S.D. from six rats in each group. *As compared to normal $p<0.05$ (Student's t-test). **As compared to ethanol-treated, $p<0.05$ (Student's t-test).

Source: From Suja Pandian et al., *J. Ethnopharmacol.*, 81:393–397, 2002. With permission.

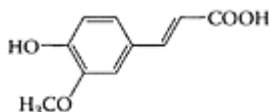
Tiran (2003) cautioned women with such preexisting conditions as gastrointestinal upset, diabetes, hypertensive disease, and cardiac disease or who are breast-feeding against using fenugreek.

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Ferulic acid

Ferulic acid, found widely in fruits and vegetables, has strong antioxidant properties against peroxynitrite (Pannala et al., 1998) and oxidized low-density lipoprotein *in vitro* (Schroeder et al., 2000). Kanski and coworkers (2002) showed ferulic greatly reduced free-radical damage in neuronal-cell systems without causing cell death by protecting them against oxidative stress from hydroxyl and peroxy radicals. This study pointed to the importance of natural antioxidants, such as ferulic acid,



Ferulic acid. (Adapted from Pannala et al., *Free Rad. Biol. Med.*, 24:594–606, 1998.)

TABLE F.29

Incidence and Multiplicity of Intestinal Tumors in Each Group¹

Treatment	No. of Rats	Incidence ² (%) and Multiplicity (Number in Parentheses)		
		Entire Intestine	Small Intestine	Large Intestine
(1) AOM alone	22	68(1.00±0.90)	23(0.32±0.63)	59(0.68±0.63)
(2) AOM+250 ppm FA ³	22	32 ⁵ (0.36±0.57)	5(0.05±0.21)	32(0.32±0.47) ⁶
(3) AOM+500 ppm FA ³	22	36 ⁶ (0.45±0.72) ⁵	5(0.05±0.21)	32(0.41±0.72)
(4) AOM+250 ppm FA ⁴	22	55(0.64±0.64)	23(0.23±0.42)	41(0.41±0.49)
(5) AOM+500 ppm FA ⁴	22	11 (0.68±0.76)	27(0.27±0.45)	36(0.41±0.58)
(6) 500 ppm FA alone	16	0	0	0
(7) No treatment	16	0	0	0

¹AOM given once a week for three weeks at a dose of 15 mg/kg.

²No. of rats with colonic tumors/no. of rats examined.

³FA (Ferulic acid) exposure during initiation of the phase.

⁴FA (Ferulic acid) exposure during the postinitiation phase.

⁵Significantly different from AOM alone; $p<0.03$.

⁶Significantly different from AOM alone; $p<0.01$.

⁷Significantly different from AOM alone; $p<0.05$.

Source: From Kawabata et al., *Cancer Lett.*, 157:15–21, 2000. With permission.

as a therapeutic agent against neurodegenerative disorders, such as Alzheimer's disease. A novel chemical derivative of ferulic acid (FA 15) made by Murakami et al. (2000) to suppress phorbol ester-induced Epstein-Barr virus activation and superoxide anion generation *in vitro*. Murakami and coworkers (2002) later showed that, unlike ferulic acid, FA 15 significantly attenuated phorbol ester-triggered hydrogen-peroxide production, edema formation, and papilloma development in ICR mouse skin. The ferulic-acid derivative, FA 15, appeared to be a novel chemopreventive agent.

Ferulic acid was also a potent inhibitor of mutagenesis and carcinogenesis induced by polycyclic aromatic hydrocarbon. For example, ferulic acid prevented 4-nitroquinoline 1-oxide (4-QO)-induced tongue carcinogenesis in rats (Tanaka et al., 1993) and depressed TPA-induced skin tumorigenesis and pulmonary cancers in mice (Asanoma et al., 1994;

Lesca, 1983). Kawabata et al. (2000) reported dietary ferulic acid significantly reduced the total number of aberrant crypt foci (ACF) in the colon of azoxymethane-treated (AOM) male rats. The incidence and multiplicity of intestinal neoplasms were also significantly reduced, as shown in Table F.29. The values obtained in the intestine, in the presence of ferulic acid, tended to be lower compared to treatment with AOM alone. The multiplicity of tumors in the entire intestine was significantly reduced in groups 2 and 3, in the large intestine in group, compared to group 1. The blocking effect of ferulic acid on AOM-induced colon carcinogenesis appeared to be related to its significant elevation of phase II detoxifying enzymes, glutathione *S*-transferase in the liver, and quinone reductase in the liver and colonic mucosa.

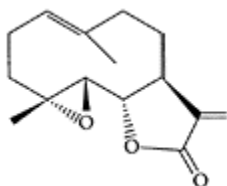
Rouau and coworkers (2003) recently detected a trimer of ferulic acid in alkali extracts of maize bran. Using 1D and 2D NMR, the structure of the trimer was identified as 4-*O*-8',5'-dehydrotriferulic acid.

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Feverfew

Feverfew (*Tanacetum parthenium* L.), an aromatic herb, has been used as folk medicine for the treatment of migraine and arthritis (Berry, 1984; Johnson, 1984). Biological activity reported in the crude extracts from feverfew leaves may explain its therapeutic and anti-inflammatory properties. Such activity includes inhibition of platelet aggregation (Groenewegen and Heptinstall, 1990) and release of histamine from mast cells (Hayes and Foreman, 1987), as well as antinociceptive and anti-inflammatory activities in mice and rats (Jain and Kulkarni, 1999). Several sesquiterpene α -methylene butyrolactones in feverfew extracts, exhibiting these properties, were identified as parthenolide and canin. Piela-Smith and Liu (2001) attributed the anti-inflammatory properties of feverfew extracts and parthenolid



Parthenolide. (From Miglietta et al., *Chemico-Biol. Interactions*, 149:165–173, 2004. With permission.)

to their ability to inhibit the expression of proinflammatory cellular-adhesion molecules in cultured synovial fibroblasts obtained from rheumatoid-arthritis patients. Figure F.39 shows feverfew extract and parthenolide both inhibited the expression of an inflammation-related adhesion molecule, VCAM-1, induced by TNF. Kwok et al. (2001) examined the molecular basis for parthenolide's ability to inhibit the proinflammatory signaling pathway. They found it bound and inhibited the I κ B kinase, a multisubunit complex responsible for cytokine-mediated stimulation of genes involved in the inflammation process. Smolinski and Pestka (2003) confirmed the anti-inflammatory properties of three herbal constituents, including parthenolide on lipopolysaccharide-induced (LPS), proinflammatory cytokine production. They found that the data from cell culture could not accurately predict the effect in animals so that animal models were still needed for confirmation. Fiebich and coworkers (2002) were the first to report parthenolide-inhibited activation of p42/44 mitogen-activated protein kinase (MAPK), which reduced the production of inducible nitric-oxide synthase (iNOS) synthesis and nitric-oxide release. Since nitric oxide is implicated in the etiology of central-nervous system (CNS) diseases, such as multiple sclerosis, their

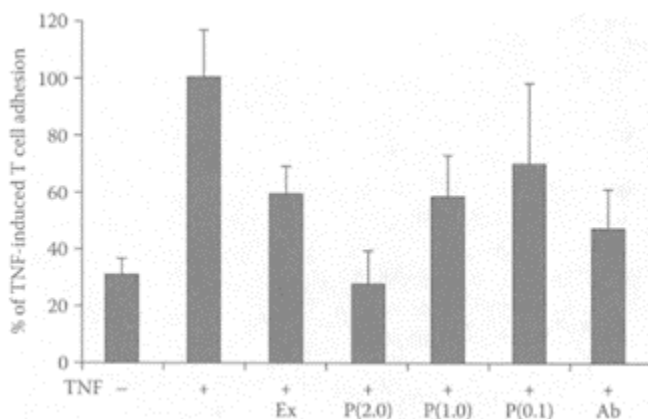


FIGURE F.39 Feverfew and parthenolide inhibition of synovial VCAM-1. Synovial FB was pretreated with feverfew extract (Ex) (1:80) or parthenolide (P) (2.0 and 1.5 $\mu\text{g/mL}$) for 4 h prior to treatment with TNF (500 $\mu\text{g/mL}$). (From Piela-Smith and Liu, *Cell Immunol.*, 209:89–96, 2001. With permission.)

results suggested parthenolide may have potential for treating CNS diseases where NO is part of the pathophysiology.

Pittler and coworkers (2000) systematically reviewed evidence for feverfew's efficacy to treat migraine. They concluded that the prevention of migraine by feverfew was still to be established. Nelson et al. (2002) showed that while the quantity of feverfew leaves in each capsule sold to consumers was similar, the parthenolide content per dosage form varied by as much as 150-fold and the percent parthenolide by 5.3-fold. The lack of standardization of feverfew products could explain the variability in efficacy.

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Fish

There have been some reported studies of an inverse relationship between fish consumption and cardiovascular disease (Kromhout et al., 1985). Ecological studies suggest an inverse relationship between the incidence and mortality from cancer and fish consumption (Caygill et al., 1996; Kaizer et al., 1989). A recent panel report that reviewed epidemiological studies concluded that fish may protect against colon, rectal, and ovarian cancers (World Cancer Research Fund, American Institute for Cancer Research, 1997). Fernandez and coworkers (1999) examined the relation between the frequency of fish consumption and the risk of certain selected types of cancers in patients in northern Italy between 1983 and 1996. Their study suggested that even a small amount of fish reduced the risk particular of digestive-tract cancers.

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Fish oil

see also Docosahexaenoic and Eicosapentaenoic acids Fish oils are rich in polyunsaturated fatty acids (PUFAs), particularly ω -3 fatty acids, which are known to reduce cholesterol. Chen and Auburn (1999) showed docosahexaenoic acid (DHA) in fish oil selectively inhibited the growth of human papillo-marvirus (HPV) type 16 compared to eicosapentaenoic acid (EPA). These inhibitory effects were mediated via lipid peroxidation as α -tocopherol abrogated the effects of DHA. Liu et al. (2001) showed that a daily intake of a small amount of fish oil in bread fed to hyperlipidemic subjects significantly increased omega-3 fatty acids and HDL cholesterol levels, while decreasing triglycerides and malondialdehyde levels, reducing the risk of cardiovascular disease. A single-center, eight-month, randomized, double-blind, placebo-controlled study of 206 healthy nonsmoking subjects by Khan et al. (2003) showed the beneficial effects of fish oil on endothelial function. An increase of 6 percent EPA and 27 percent DHA in the diet, equivalent to eating oily fish two to three times per week, may significantly improve cardiovascular function and health.

In vitro studies with PUFAs from fish oil were found to enhance the efficacy of chemotherapeutic drugs against different cancer-cell types, such as MDA-MB 231 breast-cancer cells (Hardman et al., 1997), leukemic cells (De Salis and Meckling-Gill, 1995), and THKE tumorigenic human kidney epithelial cells (Maehle et al., 1995). The growth of human A549 lung-cancer cells, implanted subcutaneously on the backs of nude mice, was studied by Hardman and coworkers (2000a), who examined the change in the diet to 20 percent corn oil or 19 percent fish oil/1 percent corn oil on tumor growth. The growth of tumors was divided into two phases: phase I included the first 10 days on corn oil or fish diets plus four days for initiation of treatment with doxorubicin (DOX), commonly used in chemotherapy. Phase II commenced on the 14th day to allow sufficient time for DOX treatment to effect tumor size. No significant differences were observed in the rate of tumor growth in phase I, irrespective of the diets. During phase II, however, the tumors in animals consuming the fish-oil diet treated with iron and DOX were significantly regressed (Table F.30). In sharp contrast, the tumors in animals fed corn oil and treated with iron and DOX continued to grow. This study confirmed the potential benefit of

TABLE F.30

Growth Rate of A549 Human Lung Tumors (Mean mm³ Per Day+SD of Slope)

Final Diet/Treatment Group (n=5)	Phase I ^a	Phase II
1) Corn oil; DOX	14.8±1.9	-1.5±1.8 ^b
2) Fish oil; DOX	16.2±1.8	-11.1±1.5 ^c
3) Corn oil+iron; DOX	15.9±1.3	34.1±4.2 ^d
4) Fish oil+iron; DOX	11.2±2.3	-13.1±4.2 ^c
5) Corn oil; no DOX	14.9±2.0	14.9±2.0 ^e

^aLinear-regression analyses showed that during phase I, all slopes were significantly different from 0. ANOVA of the slopes showed that the growth rates of the tumors (slopes) were not significantly different from each other during phase I, when mice were consuming either a corn-oil or a fish-oil diet without added iron and without DOX treatment. b,c,d,eLinear-regression analyses showed that the tumor-growth rate (slope of the regression line) of the group of mice that consumed corn oil and was treated with DOX was not significantly different from a slope of 0. The tumor-growth rate of all other groups was a significant positive or negative slope. ANOVA, followed by Tukey's multiple comparisons test of the slopes, showed that growth rates (slopes) with the same letter are not significantly different, while growth rates with different letters are significantly different.

Source: From Hardman et al., *Cancer Lett.*, 158:109, 2000b. With permission.

fish oil as an adjuvant in the treatment of cancer. A combination of fish oil and butyrate-producing fiber pectin was shown by Hong and coworkers (2002) to upregulate apoptosis in colon cells exposed to the carcinogen azoxymethane. This effect was attributed to the oxidation of unsaturated mitochondrial lipids in fish, leading to an increase in reactive-oxygen species.

A recent study by Pedersen and coworkers (2003) showed fish oil increased *in vivo* oxidation and *in vitro* susceptibility of LDL particles to oxidation in type 2 diabetic patients, characteristic of proatherogenic behavior. This contrasts with the beneficial effects that fish oil has on inflammation and heart disease, requiring more studies to establish its clinical significance.

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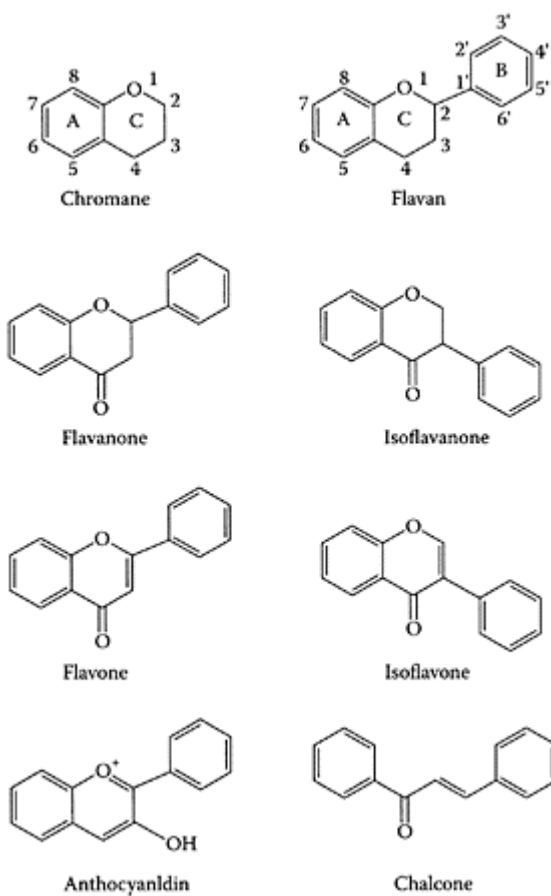
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Flavonoids

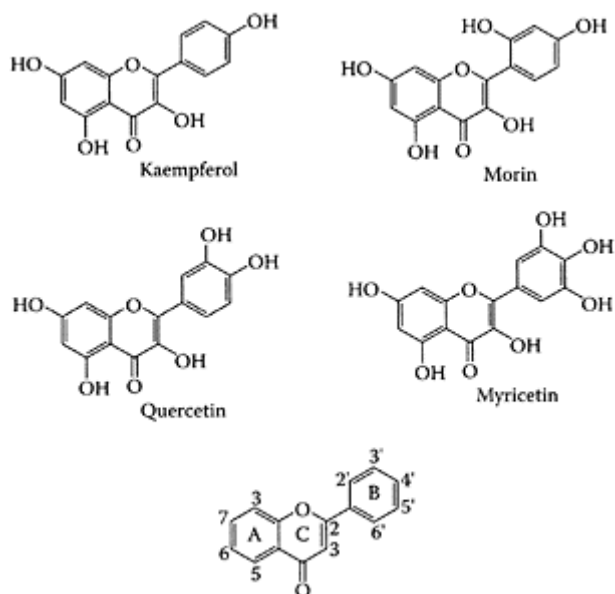
Flavonoids include a diverse group of more than 8000 polyphenolic compounds responsible for the antioxidant properties of fruits, vegetables, and herbs. The average daily intake of flavonoids in our diet was estimated to be around 1 g (Pierpoint, 1986). Flavonoids can be classified into eight groups, shown by their different basic skeleton structures, shown in Scheme F.22.

Examples of flavonoids are quercetin, myricetin, kempferol, and morin, characterized by a common ring structure, or flavone, but differing in the number and location of hydroxyl groups (Scheme F.23).

Zhu et al. (1999) found quercetin was most effective in protecting LDL from oxidation, followed by myricetin. Kampferol and morin exerted similar but much-less-protective effects, while ascorbic showed little or no effect (Figure F.40). Differences in efficacy among various flavonoids appeared to be related to the number and location of hydroxyl groups on the B ring and their stability in sodium-phosphate



SCHEME F.22 Structures of basic flavonoid skeletons. (From Hodak, et al., *Chem. Biol. Interact.* 139:1–21, 2002. With permission.)



SCHEME F.23 Structures of kaempferol, morin, quercetin, and myricetin. (From Zhu et al., *J. Nutr. Biochem.*, 11:14–21, 2000. With permission.)

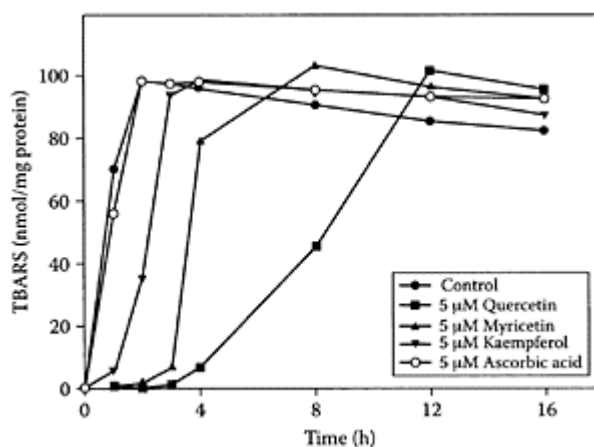


FIGURE F.40 Inhibitory effect of four flavonoids on the production of TBARS in Cu^{2+} -mediated oxidation of

human low-density lipoprotein (LDL).
Data expressed as means \pm SD of five
samples. (Zhu et al., *J. Nutr. Biochem.*,
11:14–21, 2000. With permission.)

buffer. This was confirmed in a recent study by Peng and Kuo (2003), which also found antioxidant activity was much stronger in quercetin and myricetin because of their *o*-dihydroxyl or vicinal-trihydroxyl groups. Kampferol, with a single hydroxyl in the B ring, did not protect Caco-2 cells from lipid peroxidation. The ability of flavonoids to scavenge peroxynitrite, a cytotoxic intermediate formed from superoxide anion and nitric oxide, was also shown by Choi et al. (2002) to be dependent on the position of the hydroxyl group. Quercetin with an *ortho*hydroxyl structure was the most potent scavenger, with an IC₅₀ of 0.93 μ M.

The neuroinflammatory disease multiple sclerosis (MS) is characterized by demyelination. A recent study by Hendriks et al. (2003) showed flavonoids had therapeutic potential because of their ability to limit the demyelination process in the myelin of adult mice brain tissue. The most effective flavonoids were quercetin, luteolin, and fisetin, with hydroxyl groups at the B-3 and B-4 positions in combination with a C-2, 3 double bond.

Kobayashi and coworkers (2002) showed flavonoids were potent regulators of cyclin B and p21 for cell-cycle progression in human LNCaP prostate-cancer cells, and could play a preventative role in carcinogenesis.

In a review of flavonoids, Hodek et al. (2002) pointed out that while many of them exert beneficial effects, some may have mutagenic and prooxidant effects. Interaction of some flavonoids with cytochrome P450 (CYP) can result in enhanced activation of carcinogens or influence drug metabolism. In contrast, however, other flavonoids may have a beneficial effect by inhibiting activation of carcinogens by CYPs. Interaction of some flavonoids with prescribed drugs can lead to altered pharmacokinetics by either increasing their toxicity or reducing their therapeutic effects, depending on their structure (Tang and Stearns, 2001). For example, naringenin and bergamottin in grapefruit juice can lead to impaired hepatic metabolism of certain drugs (He et al., 1998; Bailey et al., 2000). The indiscriminate use of herbal products containing a wide range of flavonoids can similarly affect the efficacy and toxicity of drugs.

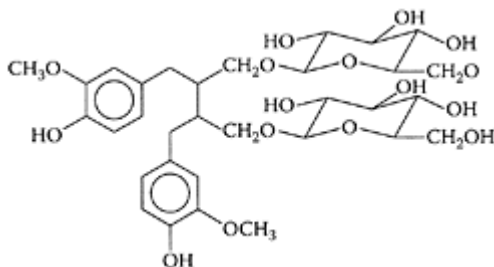
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Flaxseed

Flaxseed is obtained from flax (*Linum usitatissimum*), a versatile, blue-flowered crop. The seed, flat and oval with a pointed tip, is rich in protein, fat, and dietary fiber. Flaxseeds are one of the richest sources of the omega-3 fatty acid α -linolenic acid (ALA) (Oomah and Mazza, 2000). In addition, flaxseeds are also rich in phenolic compounds, particularly lignans, and dimers with a 2,3-dibenzylbutane structure (Harris and Haggerty, 1993). The lignan precursor in flaxseed is secoisolariciresinol diglycoside, or SDG, which appears to have some important health benefits. Yan et al. (1998) showed that supplementation of flaxseed in the diet reduced metastasis, the spread of malignant cells, in experimental mice with melanoma cells. Further work by Li et al. (1999) showed that dietary supplementation with SDG significantly decreased the number of lung tumors (Table F.31). In the control group, 59 percent (16 out of 27) of the mice had >50 tumors compared to 30, 21, and 22 percent of mice fed diets containing 73, 147, and 293 $\mu\text{mol/kg}$ SDG. A significant decrease in tumor cross-sectional area and volume were also observed with SDG-fed mice in a dose-dependent manner. Dabrosin and coworkers (2002) found that the addition of 10 percent flaxseed in the diet of nude mice with human breast-cancer xenografts showed a reduction in tumor growth and metastasis.



Secoisolariciresinol diglycoside. (From Rickard et al, *Cancer Lett.*, 161:47–55, 2000. With permission.)

TABLE F.31

Effect of Dietary Supplementation with SDG on Pulmonary Metastasis Cells in Mice

	Control					
	Mice with Lung Tumors			Tumors/Mouse		
	N	1–50 tumors	>50 tumors	Median ^a	Mean±SE	Range
Control	27	11	16	62	64±8	10–180
SDG						
73 µmol/kg	27	19	8	38	43±5	8–117
147 µmol/kg	28	22	6 ^a	36	42±4	9–96
293 µmol/kg	27	21	6 ^a	29 ^b	33±4	4–86

^aSignificantly different from the control, $p\leq0.05$. Data analyzed using Fisher’s exact test.

^bSignificantly different from the control, $p\leq0.01$. Data analyzed using Kruskal-Wallis nonparametric and Duncan’s multiplecomparison tests.

Source: From Li et al., *Cancer Lett.*, 142:91–96, 1999. With permission.

The presence of ALA in flaxseed appeared to protect against cardiovascular disease (Allman et al., 1995; Ferretti and Flanagan, 1996). Consumption of flaxseed either raw or defatted was shown to reduce total and LDL cholesterol in human subjects (Cunnane et al., 1993; Jenkins et al., 1999). Flaxseed oil was also found to be a potent inhibitor of proinflammatory mediators (Caughey et al., 1996; James et al., 2000). Flaxseed gum reduced blood-glucose response, as it behaved like a viscous fiber, while flaxseed protein interacted with the gums, as well as stimulated insulin secretion, reducing the glycemic response. Studies clearly showed flaxseed was an important functional food capable of slowing down the progression of many degenerative diseases (Oomah, 2001). A recent study by Bhathena and coworkers (2003) found flaxseed was more hypotriglyceridemic and hypocholesterolemic than soybean-protein concentrate. Consequently, flaxseed could provide an alternative, therapeutic treatment for individuals suffering from hypertriglyceridemia and hypercholesterolemia.

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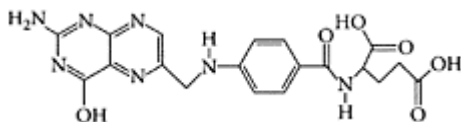
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Folic acid

An important therapy for treating advanced colorectal and other cancers involves a combination of leucovorin and fluorouracil (Mini et al., 1990; Buroker et al., 1994; Trave et al., 1988). The potentiation between leucovorin and fluorouracil is associated with the formation of the metabolite methylenetetrahydrofolate (CH_2FH_4) (Dohden et al., 1993; Raghunathan et al., 1997) Since folic acid, an



Folate. (Adapted from Park et al., *Biomaterials*, 26:1053–1061, 2005.)

important B vitamin, can also elevate CH₂FH₄ levels, Raghunathan and Priest (1999) examined its ability to modulate the antitumor activity of fluorouracil. Implanted mouse mammary adenocarcinoma tumors were allowed to grow in mice maintained on a folic acid-depleted diet for 10 days. Folic acid (45 mg/kg) or fluorouracil (10 mg/kg) diluted in sterile saline solution were then injected i.p. The results in Table F.32 show that fluorouracil alone inhibited tumor growth by around 25 percent. In contrast, folic acid enhanced tumor growth almost twofold.

TABLE F.32

Folic-Acid Potentiation of Flourouracil Antitumor Activity¹

Folic Acid (mg/kg)	Flourouracil (mg/kg)	Tumor Growth (mg/kg)
0	0	920±69
0	10	694±55
45	10	259±16
45	0	1829±218

¹Values represent the means±SEM from five mice.

Source: From Raghunathan and Priest, *Biochem. Pharmacol.*, 58:835–839, 1999. With permission.

However, when folic acid was administered 4 h prior to fluorouracil, to maximize accumulation of CH₂FH₄ and tetrahydrofolate (FH₄), tumor growth was significantly ($p<0.001$) reduced by more than 70 percent. This study confirmed the ability of folic acid to potentiate the antitumor effects of fluorouracil. Folate status is now recognized as a factor in the prevention of carcinogenesis (Kim, 1999). A deficiency in folate is thought to increase the risk of malignancy by either DNA hypomethylation and proto-oncogene activation or by inducing uracil misincorporation, resulting in DNA breakage and chromosomal damage (Duthie, 1999). Recent studies pointed to an association between higher dietary folate and reduced breast-cancer risk in women with high alcohol intake (Zhang et al., 1999; Rohan et al., 2000; Negri et al., 2000; Sellers et al., 2001). The primary circulating form of folate is 5-methyl-enetetrahydrofolate, which is produced from 5,10-methylenetetrahydrofolate by the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR). In a case-control study with 62 women, Sharp et al. (2002) showed MTHFR polymorphisms may be modifiers of the relationship between dietary folate and breast cancer. While the number of subjects in this study was small, there was a trend between increasing folate intake and decrease in the risk of breast cancer. A recent study by Plaschke et al. (2003), however, was unable to find a similar association between high MTHFR activity and colorectal cancer.

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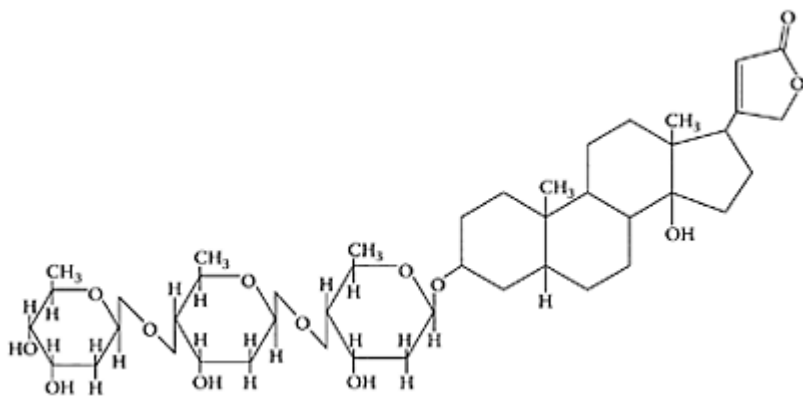
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Foxglove (*Digitalis purpurea*)

Foxglove first came into prominence more than 200 years ago when William Withering reported the efficacy of its leaves in treating congestive heart failure. Subsequent work,

using the flouometric microculture cytotoxicity assay, isolated a relatively high-molecular-weight fraction in the ethanolic extract of foxglove with potent antitumor activity (FMCA) (Larsson et al, 1992). This fraction was identified as digitoxin, a steroidal compound characterized by a five-membered, unsaturated lactone ring, belonging to a group of cardiac glycosides known as cardenolides. Another member of this group is digoxin. A second group of cardiac glycosides containing a six-membered, unsaturated lactone ring was also identified and referred to as bufadienolides. Of the latter, the therapeutically most important one is proscillaridin A. Digitalis, or cardiac glycosides, refer to any steroidal glycoside compounds that cause characteristic positively inotropic (increase in maximum and velocity of myocardial contractile force associated with prolongation of relaxation period) and electrophysiological effects on the heart. Evidence strongly suggests that cardiac glycosides induce increases in intracellular Na^+ concentration or activity in which digitalis induces a positive inotropic effect.

The first large-scale, placebo-controlled mortality study to examine the effect of digoxin on 7788 patients suffering from chronic heart failure was conducted by Gheorghiade (1997). While digoxin had no effect on their survival, over 37 months of follow-up, the incidences of hospitalization due to worsening of heart failure were significantly lower in patients receiving digoxin compared to the placebo. Digoxin, the most commonly prescribed of the various cardiac glycoside preparations, was reported by Hauptman (1999) to be still useful for treating heart failure. Using primary cultures of tumor cells from patients and a human cell-line panel, Johansson et al. (2001) evaluated the cytotoxicity of five cardiac glycosides plus the saponin digitoxin and its aglycone digitoxigenin. Marked differences were observed among the different cardiac glycosides, with respect to their toxicities. Proscillaridin A proved to be the most potent in 9 of 10 human tumor lines, confirming the literature that cardenolides are



Structure of digitoxin. (From Hage and Sengupta, *J. Chromatogr. B.*, 724:91–100, 1999. With permission.)

weaker than the corresponding bufadienolides. The order of potency, after proscillaridin A, was digitoxin, ouabain, digoxin, lanatoside C, digitoxigenin, and digitonin, which paralleled their inhibitory potency on Na^+/K^+ -transporting ATPase from human cardiac muscle reported previously for cardiac glycosides by Schonfeld et al. (1986). Reviewing

the use of digitoxin as a treatment of congestive heart failure, Beltz et al. (2001) showed digitoxin exerted the same pharmacodynamic kinetics as digoxin. However, digitoxin was more lipophilic than digoxin, giving it a more stable pharmacokinetic profile and a lower incidence of toxic side effects. Roever and coworkers (2000) had shown previously that digitoxin had a lower rate of toxicity compared to digoxin when used by elderly patients. Patients taking digoxin had three times the odds of experiencing toxicity compared to digitoxin.

Cardiac glycosides can interact with other drugs, so caution must be exercised when introducing new pharmaceuticals. For example, quinidine inhibited the transport of digoxin across the cell membranes, particularly in the kidneys (Fromm et al., 2002), while amiodarone increased the steady state of digoxin so that dosages could be decreased by as much as 50 percent.

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Fruits

see also Individual fruits A large number of epidemiological studies have associated the low incidence of common cancers, cardiovascular disease, and other chronic diseases to the high consumption of fruits and vegetables (Ness and Powles, 1997; Steinmetz and

Potter, 1996). Lampe (1999) reviewed the many human studies in which phytochemicals identified in fruits and vegetables were investigated in an effort to assess their mechanisms of action. A large, prospective, cohort study of 39,876 female health professionals over a five-year period by Liu and coworkers (2000) indicated that a higher intake of fruits and vegetables may have a protective effect against cardiovascular disease. This is attributed to the naturally occurring antioxidants scavenging free radicals and preventing degenerative diseases, such as cancer, atherosclerosis, diabetes, and arthritis (Kaur and Kapoor, 2001). Thompson and coworkers (1999) showed that increased consumption of fruits and vegetables by a group of women significantly decreased the levels of urinary 8-hydroxydeoxy-guanosine (8 OhdG), malondialdehyde (MDA), and 8-isoprostane F-2 α , all markers of oxidative cellular damage. The data generated by this study showed that increased fruit and vegetable consumption did in fact reduce cellular injury, as measured by these biomarkers. Broekmans et al. (2000) were the first to demonstrate that fruits and vegetables with moderate folate levels decrease plasma homocysteine, a risk factor for cardiovascular disease.

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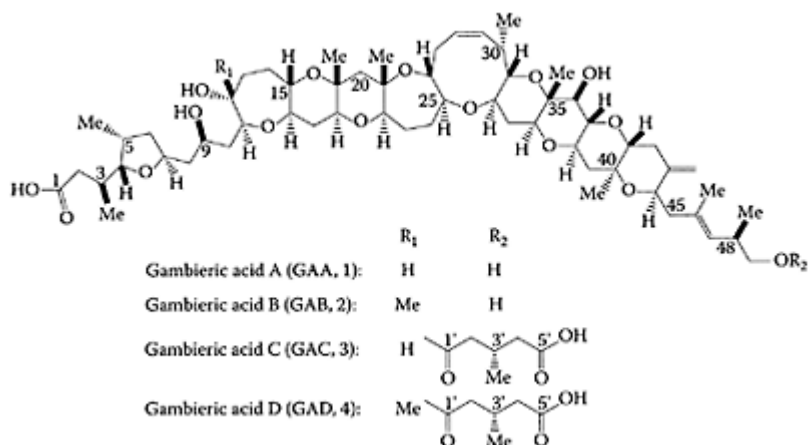
Gambieric acids

Gambieric acids A-D are potent, antifungal compounds obtained from the marine dinoflagellate *Gambierdiscus toxicus* (Nagai et al., 1992). The antifungal activity of these ladder-shaped polyethers against *Aspergillus niger* is 2000 times greater than that of amphotericin B. Morohashi et al. (2000) determined the absolute configuration of gambieric acids A-D as shown in Scheme G.24.

Gambierdiscus toxicus also produces other polyethers, such as brevetoxins and ciguatoxins, which are highly toxic. These compounds exert their neurotoxicity by binding to a specific site on the voltage-gated sodium channels of excitable membranes (Catterall, 2000), referred to as site 5. Inoue and coworkers (2003) recently showed that gambieric acid-A, a nontoxic polyether, inhibited the binding of brevetoxin to site 5.

References

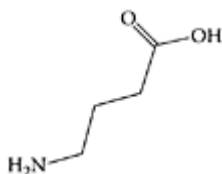
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SCHEME G.24 Structures of gambieric acids A-D. (From Morohashi et al., *Tetrahedron*, 56:8995–9001, 2000. With permission.)

Gamma amino butyric acid (GABA)

The amino acid γ -amino butyric acid (GABA) is produced primarily by decarboxylation of glutamate by glutamate decarboxylase, a vitamin B₆-dependent enzyme. Found in many fruits and vegetables, GABA was reported



Gamma amino butyric acid (GABA). (From Mohorashi et al., *Tetrahedron*, 56:8995–9001, 2000. With permission.)

almost 50 years ago to reduce blood pressure in animals and man (Takahashi et al., 1953; Elliott and Hobbiger, 1959). This property was due, in part, to its ability to block peripheral ganglia (Stanton, 1963). Using hypertensive rats, Hayakawa and coworkers (2002) showed the antihypertensive effect of GABA involved possible inhibition of noradrenaline release from sympathetic nerve endings. Recent work by Inoue et al.

(2003) examined the effect of a new, fermented-milk product containing GABA on mildly hypertensive patients. A randomized, placebo-controlled, single-blind trial on 39 mildly hypertensive patients (16 women and 23 men), ranging in age from 28–81 years, were fed the fermented milk product over a 12-week period. A significant ($p<0.05$) decrease in systolic, diastolic, and mean blood pressure was observed after four weeks for the group fed the fermented-milk product (Figure G.41). The reduction in systolic and mean blood pressures were significantly lower for the treated group over the entire 12 weeks of the study. No side effects were observed from the intake of the fermented product, suggesting the potential of GABA-containing products for controlling blood pressure in patients suffering from mild hypertension.

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Gamma linolenic acid (GLA)

Gamma linolenic acid (GLA, C18:3 ω -6) occurs abundantly in such plant seeds as borage, evening primrose, and black currants (Eskin, 2002). The conversion of GLA from dietary linoleic acid (C18:2 ω -6) in humans is impaired, as the enzyme involved, Δ 6-desaturase, is either blocked or saturated. Consequently oral GLA has been shown to treat a number of inflammatory disorders, such as rheumatoid arthritis (Leventhal et al., 1993; Zurrier et al., 1996) and atopic dermatitis (Horrobin, 1993; Andreassi et al., 1997). The benefits associated with GLA are attributed to its interference in AA metabolism to bioactive eicosanoids (Miller and Ziboh, 1988). This appears paradoxical, as GLA is a precursor of AA, which can bring about proinflammatory events. However, Peterson et al. (1999) reported dietary GLA exerted immunoregulatory functions. These anti-inflammatory effects were found by Kaku et al. (2001) to be due to the suppression of leukotriene B₄ production by high doses of GLA.

Gillis et al. (2002) showed GLA alone, or in combination with EPA, significantly induced neutrophil apoptosis and reduced cell viability in human promyelocytic leukemia

HL-60 cells. This effect was attributed to GLA's ability to attenuate the production of leukotriene B₄ (LTB₄) by inhibiting 5-lipoxygenase (Ziboh and Fletcher, 1992). LTB₄ is crucial for neutrophil viability and chemotaxis. Using a rat-infusion glioma model, Leaver and coworkers (2002)

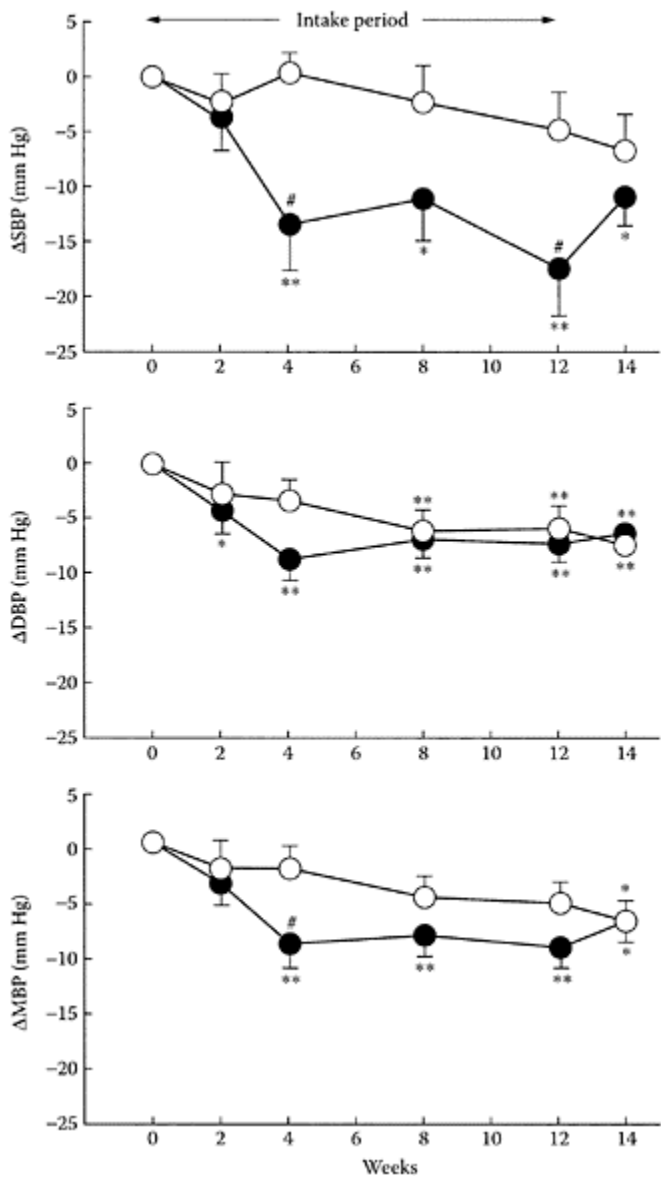


FIGURE G.41 Changes (relative to baseline values) in systolic blood

pressure (Δ SBP), diastolic blood pressure (Δ DBP), and mean blood pressure (MBP) after intake of fermented-milk product with GABA (●) or placebo (○). (From Inoue et al., *Eur. J. Clin. Nutr.*, 57:490–495, 2003. With permission.)

found slow infusion of GLA of 2 mM/L over seven days stimulated regression in tumor size and cell death in tumor implants. The potential therapeutic, safe use of γ -linolenic acid for treating human gliomas was further verified by Bakshi et al. (2003). GLA (1 mg) was administered for seven days to nine patients via a cerebral reservoir or by direct, intratumoral delivery, with grade four disease and recurrent glioma. Some improvement in patient survival was observed, with no side effects reported.

GLA has also been studied as a novel, intravesical cytotoxic agent against superficial bladder cancer (Crook et al., 2000). The instability of GLA led to its coupling with a number of agents to enhance its half-life. Harris and coworkers (2003) used the formulation of meglumine GLA (MeGLA), as meglumine is a nontoxic compound used in radiological-contrast media, to assess its efficacy in 30 patients with recurrent transitional-cell carcinoma. No local or systemic side effects were observed following treatment of 15 patients with 50 mL of either 50 mg (1 mg/mL) or 125 mg (2.5 mg/mL) of MeGLA in water. The safety and tolerability of MeGLA were confirmed, and the 43 percent response rate indicated significant cytotoxic effects against transitional-cell carcinoma.

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Ganoderma

Ganoderma is a mushroom used in Oriental traditional medicine for treating many chronic diseases (Gao and Zhou, 2003). Polysaccharides present its fruit body, mycelia, or spores of *Ganoderma* are pharmacologically active and include β -D-glucans, heteropolysaccharides, and glycoproteins. A fucose-containing glycoprotein isolated from *Ganoderma lucidum* was shown to stimulate spleen-cell proliferation and cytokine expression (Wang et al, 2002). Over 100 triterpenoids were isolated from *Ganoderma lucidum* including the highly oxidized lanostane-type triterpenoids, such as ganoderic and lucidenic acids. Cancer-preventive action by *Ganoderma* was attributed to the antiproliferative properties of its triterpenoids by inducing apoptosis (Birt et al., 2001; Gan et al., 1998).

Ganoderma products are sold as a single agent or with other herbal medicines. Clinical studies on prostate cancer patients using a combination of *Ganoderma* and eight herbs (PC-SPES) showed a significant reduction in the prostate-specific antigen (PSA) levels (Small et al., 2000). *In vitro* and *in vivo* studies on *Ganoderma* attributed its anticancer effects to antioxidative, free-radical scavenging, enhancement of the immune system, cell-cycle arrest, and apoptosis.

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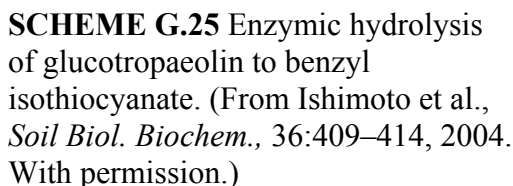
Garden cress (*Lepidium sativum*)

Garden cress is fairly unique among the *Brassica* vegetables, as it contains only one glucosinolate, namely glucotropaeolin (GT) (Fenwick et al., 1983). This glucosinolate is then hydrolyzed by the enzyme myrosinase to yield the corresponding isothiocyanate, benzylisothiocyanate (BITC) (Scheme G.25). Glucosinolates have been shown to protect laboratory animals from chemically induced cancers by inhibition of phase I enzymes or by induction of glutathione S-transferase (Chung et al., 1992; Knasmuller et al., 1996; Zhang and Talalay, 1994).

Kassie and coworkers (2002) examined the chemoprotective properties of garden cress toward the genotoxic effects of the heterocyclic aromatic amine, 2-amino-3-methylimidazo[4,5-f] quinoline (IQ), in F344 rats. Garden-cress juice reduced the IQ-induced genotoxic effects and colonic-preneoplastic lesions by the induction of UDP-glucuronosyltransferase (UDPGT), a key enzyme in the detoxification of heterocyclic aromatic amines. Kassie et al. (2002) found that the amount of juice needed to produce these changes was quite small but similar to the level of glucosinolates consumed in a regular salad.

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Garlic

In addition to being a flavoring agent, garlic (*Allium sativum* L.) is also pharmacologically active against microbial infection, thrombosis, hypertension, hyperglycemia, hyperlipidemia, and cancer. The pharmacological properties of garlic, such as lipid-lowering effects, appear to be related to sulfur-rich compounds, particularly allicin. Shukla and Taneja (2002) clearly showed the antimutagenic effects of garlic extract (GE) in Swiss albino mice using an “*in vivo* chromosomal aberration assay.” Pretreatment with 2.5 percent and 5 percent GE significantly suppressed chromosomal aberrations in cyclophosphamide (CP)-treated (a well-known mutagen) mice. The anticytotoxic effects of GE were demonstrated by a significant increase in mitotoxic index, as well as reduction in CP-induced clastogenicity. Sengupta et al. (2002) also showed that garlic constituents protected Swiss mice from DMBA-induced clastogenicity by significantly reducing chromosomal aberrations in the bone marrow. Iimuro and coworkers (2002) found that a garlic extract suppressed *Helicobacter pylori*-induced gastritis in Mongolian gerbils. Infection by this organism has been associated with the development of stomach cancer so that garlic extract appeared to be useful for reducing the risk of gastric cancer. Patients with benign prostate hyperplasia and prostate cancer

showed significant improvements after consuming an aqueous garlic extract (1 mL/kg weight) for a month (Durak et al., 2003). In addition to reducing the mass of prostate, the urinary frequency was decreased, while maximum and average rates of urine flow increased. Cancer patients had significantly lower PSA values after consumption of the garlic extract.

Epidemiological data showed an inverse relationship between garlic consumption and reduced risk of cardiovascular disease (Kendler, 1987; Keys, 1980). In their review of garlic and cardiovascular disease, Banerjee and Maulik (2002) pointed to the need to identify specific components responsible for its cardioprotective effects. Ozturk et al. (1994) observed the beneficial effects of garlic extract on vascular responsiveness in normal rats. A recent study by Baluchnejadmojarad et al. (2003) showed an aqueous garlic extract significantly improved impaired endothelium-dependent relaxations, as well as decreased the enhanced contractile response to phenyl epinephrine in diabetic rats.

Fresh garlic was reported to lower blood pressure in spontaneously hypertensive rats (Foushee et al., 1982). Further researchers confirmed the ability of garlic to control mild hypertension. Al-Quattan et al. (1999) examined the effectiveness of garlic in treating more severe hypertension, such as in unilateral renovascular hypertension (URVH). Using a 2K1C hypertensive rat, they showed that a single dose had a maximum antihypertensive effect 2–6 h after administration, continuing for up to 24 h (Table G.33). Multiple doses of garlic also controlled the rise in blood pressure in these hypertensive rats. Sharif et al. (2003) showed a negative correlation between garlic, blood pressure, and angiotensin-converting enzyme (ACE) using the same 2K1C hypertensive model. An enteric-coated garlic-powder supplement suggested that the ability of garlic to lower blood pressure was attributed, in part, to a reduction in ACE activity.

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TABLE G.33

Effect of a Single Dose of Garlic (50 mg/kg) on the Systolic Blood Pressure of Clipped Rats

Time	Water-Fed ¹ control (mmHg±SD)	Garlic-Fed ¹ (mmHg±SD)
Preclipping	123±19	121±15
Postclipping (preadministration)	135±18	132±8
30 min	141±21	128±9
2h	140±20	117±9

6h	139±16	117±5*
24 h	140±17	131±6
48 h	147±13	141±15

¹Five rats were used in each group. * $p \leq 0.05$ compared with water-treated animals at the same time.

Source: From Al-Quattan et al., *J. Ethnopharmacol.*, 66:217–222, 1999. With permission.

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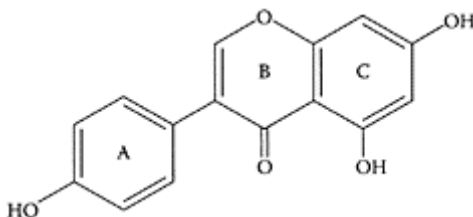
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Genistein

One of the main isoflavone components in soy is genistein. It is a phytoestrogen and an antioxidant and acts on osteoblast-like cells, increasing cellular proliferation. Lee and coworkers (2001) found genistein stimulated cell proliferation, as well as protected against oxidative damage to osteoblast-like cells from the action of free radicals. Epidemiological evidence suggests the low incidence of prostate cancer among Asians is associated with a high intake of soy. Studies conducted by Wang et al. (2002) showed that dietary genistein suppressed chemically induced prostate cancer in Lobund Wistar

rats. Po and coworkers (2002a) found genistein was not as effective in suppressing estrogen-receptor sites or inducing apoptosis



Genistein. (Adapted from Xu et al., *Structure*, 12:2197–2207, 2004.)

using a transient transfection mouse model. Confirmation of the inability of soybean genistein to exert its chemoprotective effect through antagonizing the estrogen receptor was provided by Po et al. (2002b). Soybean genistein was also found by Hewitt and Singletary (2003) to inhibit adenocarcinoma tumor growth in a syngeneic mouse model. However, the greater inhibition by the soy extract compared to genistein suggested the presence of other components besides genistein.

The induction of apoptosis in a variety of cancer-cell lines by genistein is well-established (Lian et al., 1998; Shao et al., 1998). Recent research by Baxa and Yoshimura (2003) showed that genistein induced inhibition of NF- κ B by cleaving I κ B α (Figure G.42). The latter is a protein residing in the cytosol, where it associates with NF- κ B. These researchers also showed that caspase activity was involved in cleaving I κ B α in genistein-treated cells. This was evident by a significant elevation of caspase-3 activity observed in genistein-treated T lymphoma 92316T cells after 6 h compared to the untreated cells. Other possible activities by genistein, such as inhibition of tyrosine kinase, which also reduces NF- κ B, cannot be ruled out.

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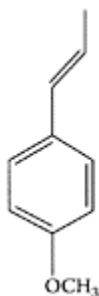
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Geraniol

Geraniol is an acyclic monoterpene alcohol found in the essential oils of fruits and herbs. Like many monoterpenes, geraniol has been reported to exert chemopreventive effects, including *in vivo* and *in vitro* antitumor activity against leukemia, hepatoma, and melanoma



Geraniol. (From Duncan et al., *Biochem. Pharmacol.*, 68:1739–1747, 2004. With permission.)

cells in experimental animals (Shoff et al., 1991; Yu et al., 1995; Burke et al., 1997). Carnesecchi and coworkers (2001) demonstrated for the first time that geraniol (400 μ M) inhibited the growth of a human colon cancer-cell line (Caco-2) by 70 percent. No cytotoxic effects or apoptosis were observed. The potent, antiproliferative effects of geraniol were attributed, in part, to a 50 percent decrease in ornithine decarboxylase activity, a key enzyme in polyamine biosynthesis, which is normally enhanced during carcinogenesis. Further research by these researchers (Carnesecchi and coworkers, 2002) showed that the antiproliferative effect of geraniol on Caco-2 cells was directly linked to perturbation of cell-membrane function, resulting in a 60 percent reduction of protein kinase C (PKC) activity. In addition, there was a 50 percent decrease in the active forms of p44/p42 extracellular signalregulated protein kinases (ERK), suggesting perturbation in signal-transduction pathways.

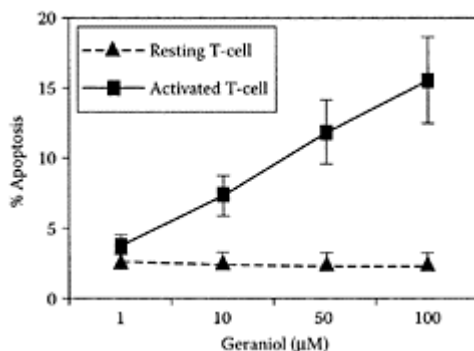


FIGURE G.43 The rat T-cells apoptosis assay, resting and activated T-cells were treated with varying concentrations of geraniol (between 1 $\mu\text{mol/L}$ and 100 $\mu\text{mol/L}$), and the activated T-cells showed higher apoptosis compared to resting cells. (From Ji et al., *Transpl. Proc.*, 34:1418–1419, 2002. With permission.)

The anticancer properties of monoterpenes were attributed to their ability to prevent isoprenylation of GTPases (Steinmetz et al., 1991). Ji and coworkers (2003) demonstrated geraniol exhibited modest immunosuppressive activity both *in vitro* and *in vivo*. This study provided the first evidence that geraniol induced apoptosis preferentially in activated T-cells (Figure G.43). Because of its suppressive property, geraniol was able to prolong graft survival in a cardiac allograft transplant model.

References

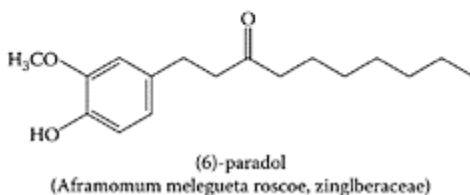
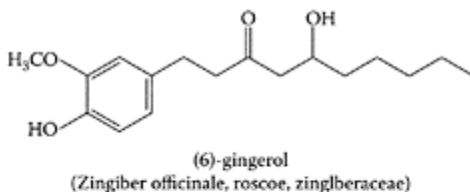
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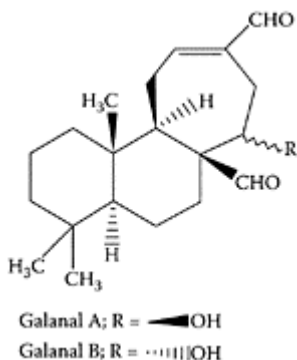
Ginger

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is used worldwide as a spice in the preparation of foods. In addition, the rhizome of ginger is a recognized treatment in traditional Oriental medicine for inflammation and rheumatism, as well as gastrointestinal problems. Koshimizu et al. (1988) found that the rhizome of ginger exerted antitumor properties by inhibiting 12-*O*-tetra-decanoylphor-bol-13-acetate (TPA)-induced Epstein-Barr virus activation in Raji cells. A later study by Katiyar and coworkers (1996) showed topical application of an ethanol extract of ginger suppressed TPA-mediated induction of ornithine decarboxylase and its mRNA expression in SENCAR mouse skin. These workers also reported that the ginger extract protected the mouse skin from 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced carcinogenesis. The protective effects of ginger have been attributed to the presence of several phenolic compounds, or vanilloids, gingerol and paradol (Locksley et al., 1972; Lee and Surh, 1998; Park et al., 1998).

Abe et al. (2002) isolated a pungent principle present in Japanese ginger (*Zingiber mioga* Roscoe) as a labdane-type dialdehyde identified as galanals A and B. Miyoshi et al. (2003)



(From Lee and Suhr, *Cancer Lett.*, 134:163–168, 1998. With permission.)



Structure of galanal A and B. (Adapted from Miyoshi et al., *Cancer Lett.*, 199:113–119, 2003.)

recently showed galanals A and B both significantly inhibited cell proliferation of human T lymphoma Jurkat cells in a dose-dependent manner (IC_{50} of 18 and 32 μM , respectively) (Figure G.44). The mechanism of apoptosis involved reduction of the Bcl-2: Bax ratio and caspase-3 activation, suggesting their potential as anticancer agents.

A recent study by Hori and coworkers (2003) isolated five sulfonated compounds from *Zingiberis rhizome* (Shokyo), 4-gingesulfonic acid, and shogasulfonic acids A, B, C, and D, together with 6-gingesulfonic acid. Their potential bioactivity remains to be examined.

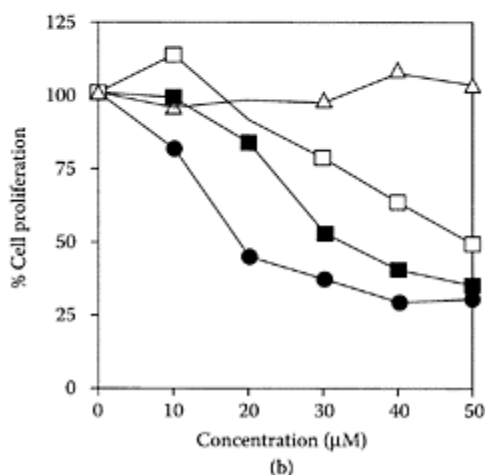
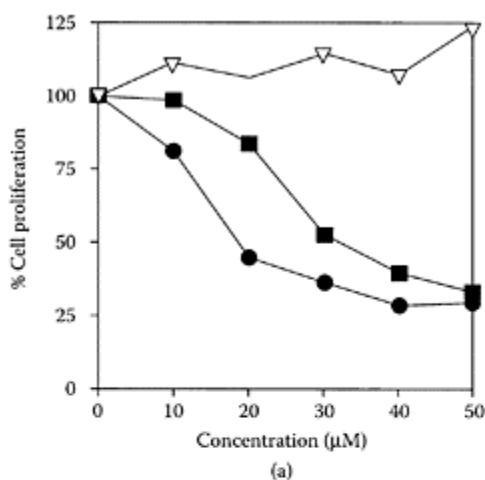


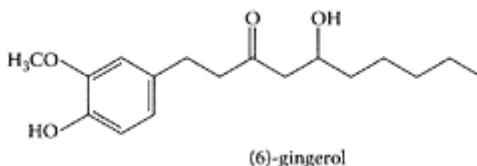
FIGURE G.44 Effect of compounds isolated from ginger plants on the cell growth of Jurkat cells. (A) Geranal A (●), galanal B (■), curcumin (□), or 6-gingerol (Δ). (Adapted from Miyoshi et al., *Cancer Lett.*, 199:113–119, 2003. With permission.)

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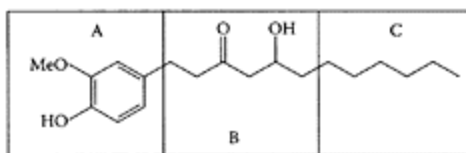
Gingerol

Gingerols are the pungent oleoresin constituents present in ginger. The major gingerol component is [6]-gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone). Isolated [6]-gingerol appeared to be



Tjendraputra, E., et al., *Bioorg. Chem.*, 29:156–163, 2001. With permission.

the active principle responsible for inhibiting secondary platelet activation and ATP release from platelets in human platelet-rich plasma. This inhibition is reversible, as it involves inhibition of arachidonic-acid metabolism and cyclooxygenase (COX) activity (Kiuchi et al., 1982; Guh et al., 1995). Koo and coworkers



SCHEME G.26 Structural features of gingerol and synthetic analogues required for COX-2 inhibition. (A) Substitution pattern on the aromatic moiety, (B) functional group substitution pattern on the side chain, and (C) the lipophilic alkyl side chain. (From Tjendraputra et al., *Bioorg. Chem.*, 29:156–163, 2001. With permission.)

(2001) showed gingerols inhibited the arachidonic acid-induced platelet serotonin release reaction in a similar dose range as aspirin. Tjendraputra et al. (2001) examined 17 oleoresin principles of ginger (*Zingiber officinale*, Roscoe) together with synthetic analogues of gingerol. They all proved potent inhibitors of COX-2 and effective for treating inflammation. Based on their relative rates of inhibition, three important structural features were required for COX-2 inhibition: (1) lipophilicity of the alkyl side chain, (2) substitution pattern of hydroxy and carbonyl groups on the side chain, and (3) substitution of hydroxy and methoxy groups on the aromatic ring (Scheme G.26).

[6]-Gingerol is a strong antioxidant, as evident by its ability to inhibit FeCl_3 -ascorbate-induced peroxidation of phospholipids (Aeschbach et al., 1994) or prevent the generation of reactive-oxygen species by xanthine oxidase (Chang et al., 1994). Park et al. (1998) demonstrated the antitumor activity of [6]-gingerol by its ability to significantly inhibit 7,12-dimethylbenz[*a*]-anthracene (DMBA)-induced skin papillomagenesis. This is shown in Table G.34 by its suppression of the tumor promoter-induced inflammation by reduction in mouse ear edema. While [6]-gingerol reduced ear edema by 61 percent, it was much less than curcumin's 91 percent reduction at the same concentration of 10 μmol .

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TABLE G.34

Inhibition of Tumor Promoter-Induced Inflammation in Mouse Ear by [6]-Gingerol^a

Test compound	Increased ear weight (g) ^a	% Inhibition
None	5.26±1.39 ^b	0
[6]-Gingerol	1.84±0.92 ^c	61
Curcumin	0.46±0.30 ^c	91

^aValues with^c are significantly different from the control ($p<0.005$).

^bValues represent the mean±SD (n=5)

Source: From Park et al., *Cancer Lett.*, 129:139–144, 1998. With permission.

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Ginkgo biloba

Extracts from the leaves of *Ginkgo biloba* L., one of the oldest phytomedicines in China, is still used extensively in therapy. The dry extract EGb 761, the essential component of *Ginkgo biloba*, is based on the content of flavonoids (24 percent) and terpenoids (6 percent). These preparations are used to treat diseases associated with advanced age, such as cerebrovascular and peripheral circulatory insufficiencies and memory disturbances (Newall et al., 1996). The extract is an effective free-radical scavenger, with antioxidant activity capable of protecting against free-radical damage associated with such diseases as arteriosclerosis, rheumatism, and cancer. The action of EGb 761 on the human brain was confirmed by electroencephalography with enhancement of the α -wave component (Itil and Martorano, 1995; Luthringer et al., 1995). Animal studies showed EGb 761 facilitated acquisition and retention of memory (Cohen-Salmon et al., 1997; Winter, 1998) through protection of the hippocampus (Barkats et al., 1995). Since Alzheimer's

disease is associated with a severely atrophied hippocampus, EGb 761 appeared to have potential as a treatment. The free-radical-scavenging effect of EGb 761 was demonstrated by the reduction of lipid peroxidation in a mouse-model brain with experimental cerebral ischemia (Pierre et al., 2002). EGb 761 prevents oxidative stress from destroying neurons, particularly by apoptosis, induced by glutamate, nitric oxide, and β -amyloid (A β) (Bastianetto and Quirion, 2002; Luo et al., 2002). Treatment of Wistar male rats with a *Ginkgo biloba* extract (GK 501) was shown by Hadjiivanova and Petkov (2002) to induce a significant decrease in the density (B_{\max}) of β -adrenoreceptors in the frontal cortex and hippocampus regions of the brain (Table G.35). Since both of these areas are involved in cognition, it suggests that treatment with *Ginkgo biloba* extract may have a beneficial effect on learning and memory.

Brayboy and coworkers (2001) showed EGb 761 protected osteoblast-like bone cells (MC3T3-E1) from free-radical damage, as well as enhanced the proliferation of these cells. Ellnain-Wojtaszek and coworkers (2002) recommended that the leaves of *Ginkgo biloba* be stored for as short time as possible to prevent loss of free-radical-scavenging activity. Several excellent reviews on *Ginkgo biloba* were recently published in a new journal on nutra ceuticals (Christen, 2003; Luo, 2003).

TABLE G.35

Effect of *In Vivo* Administration of *Ginkgo Biloba* Extract on β -Adrenergic Receptors in Different Rat Brain Regions^{a,b,c}

Brain area	Bma _x (fmol/mg pr.)	
	Control	GK 501
Cortex	322.8±21.4	228.1±29.0 ^c
Hippocampus	209.0±20.1	162.8±23.5 ^c
Hypothalamus	119.6±28.4	166.9±26.0
Stratium	209.3±23.0	226.7±21.2

^a*Ginkgo biloba* extract (90 mg/kg per day per os) or vehicle were administered for seven days.

^bResults expressed as the mean±SE for 5–10 rats.

^cSignificant difference between control and treated rats at $p<0.05$.

Source: Adapted from Hadjiivanova and Petkov, *Phytother. Res.*, 16:488–492, 2002.

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Ginseng

Ginseng, the root of *Panax ginseng*, has been used in Oriental medicine for many centuries to treat a wide range of ailments. In Europe, it is sold over the counter to enhance physical and mental performance. Ginseng products are either white or red. White ginseng is the dried root with the skin peeled off, whereas red ginseng is the steamed root, which is caramel-colored. White ginseng (includes lateral roots and root hairs) is commonly used in the European market, while red ginseng is the preferred form in Asia. The unique constituents identified in ginseng include several classes of compounds: triterpene saponins; essential oil-containing poly acetylenes and sesquiterpenes; polysaccharides; peptidoglycans; and nitrogen-containing compounds (Tang and Eisenbrand 1992). Triterpene saponins are referred to as ginsenosides, as their property appears to be a function of the number of monosaccharide residues in the sugar chain (Hostettmann and Marston, 1995). Thirty-one ginsenosides have been isolated from the roots of white and red ginseng that can be categorized into three groups, based on their aglycones, as protopanaxadiol-type, protopanaxatriol-type, and oleanolic acid-type

saponins (Sticher, 1998). Ginseng is specified in the Swiss and German pharmacopeias on the total ginsenoside content, calculated as ginsenoside Rg1, as not less than 2.0 percent and 1.5 percent, respectively. The European pharmacopeia requires that the ginsenoside R_{ga} and R_{bl} content in ginseng must not be less than 0.3 percent.

Research on ginseng suggests ginsenosides have antiaging properties by enhancing the immune system by increasing serum-specific antibodies and I_gG content and protective B-lymphocytes (Nah et al, 1995; Liu et al., 1995; Yamada et al., 1995). In addition to ginsenosides other isolated components, such as polyacetylenes, panaxytriol, panaxynol, and panaxydol have cytotoxic, antiplatelet, and antiinflammatory properties, respectively (Deng and Zhang, 1991; Matsunaga et al., 1995; Kobayashi et al., 1995). The hypoglycemic effect of ginseng is attributed to its polysaccharides, the panaxans, which are themselves peptidoglycans. Immunological activity is also associated with some of its polysaccharides, the ginsenans. While the precise structures of these polysaccharides are not fully known, their backbone chain is mainly β -1,3-linked D-galactoside (Tomoda et al., 1993).

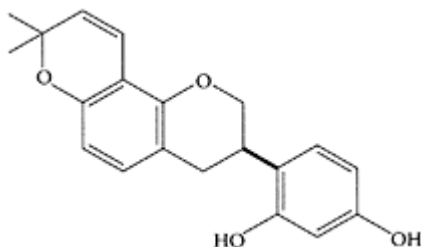
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Glabridin

Glabridin is the major isoflavan in licorice root (*Glycyrrhiza glabra*) with two hydroxyl groups at the 2' and 4' positions, a 2,2-dimethyl- γ -pyran ring fused to the B ring with a

double bond between carbon 3 and 4 in the C ring. The conjugated double-bond system present in glabridin appeared to enhance its



Glabridin. (From Fukai et al., *Fitoterapia*, 74:624–629, 2003. With permission.)

antioxidant properties, which accounted for it being the most active compound isolated from licorice that inhibited LDL oxidation (Vaya et al., 1997; Belinsky et al., 1998). Tamir et al. (2000) demonstrated the estrogenic properties of glabridin, as well as its antiproliferative properties against human breast-cancer cells. Further research by Tamir and coworkers (2001) confirmed the estrogen-like properties of glabridin but also identified a new phytoestrogen, glabrene, an isoflavene in licorice roots exhibiting stronger estrogenic agonist activity. Glabridin also affects the skin, as Yokota and coworkers (1998) found it inhibited melanogenesis and inflammation in cultured B16 murine-melanoma cells.

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Glucosamine sulfate

Glucosamine sulfate is a commonly used treatment for osteoarthritis. A three-year, randomized, placebo-controlled, double-blind study of 202 patients with knee osteoarthritis by Pavelka and coworkers (2002) showed that long-term treatment with glucosamine sulfate retarded the progression of the disease. Unlike systemic inflammatory diseases, such as rheumatoid arthritis, osteoarthritis is characterized by local inflammatory activity. A recent review by Amin et al. (1999) pointed to a local increase in the proinflammatory cytokine, interleukin-1 β (IL-1 β) during progression of osteoarthritis. IL-1 β initiates a whole series of events leading to cartilage damage, including activation of nuclear factor kappa B (Nf κ B). Using cell cultures of human osteoarthritic chondrocytes, Largo and coworkers (2003) showed glucosamine significantly inhibited Nf κ B activity, as well as the nuclear translocation of p50 and p65 proteins involved in the inflammatory process. The use of glucosamine and chondroitin sulfate for the symptomatic treatment of osteoarthritis has been controversial. Nevertheless, a recent review by Hungerford and Jones (2003) pointed to the many *in vitro* and *in vivo* animal clinical and human clinical studies that confirm both the efficacy and safety of their treatment of osteoarthritis.

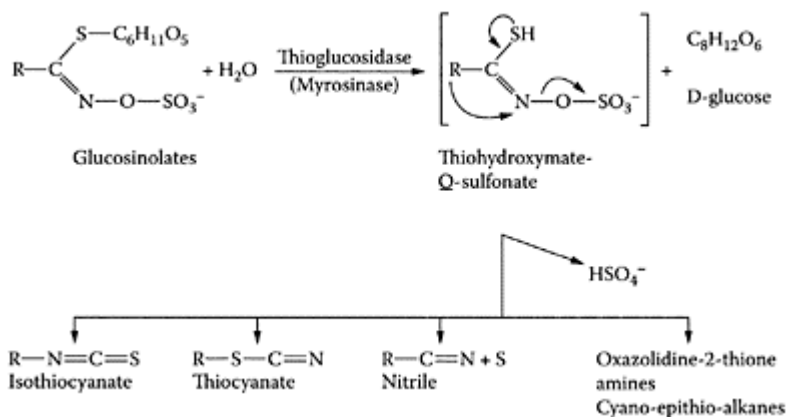
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Glucosinolates

The reduced risk of colorectal cancer associated with the consumption of cruciferous vegetables is attributed to the presence of a group of secondary plant metabolites known as glucosinolates (Verhoeven et al., 1996). These bioactive, sulfur-containing components are hydrolyzed by an endogenous plant enzyme myrosinase (thioglucoside glucohydrolase EC 3.2.3.1) to isothiocyanates. This only occurs when the cells are

broken or damaged by cutting or chewing, as myrosinase and glucosinolates are separated from each other in the intact plant. Glucosinolates are broken down into isothiocyanates, nitriles, thiocyanates, indoles, and oxazolidinethiones (Scheme G.27). Some of these degradation products, particularly the isothiocyanates (ITCs) and some indolic compounds, have health-protective effects. A typical glucosinolate is singrin, which was shown to reduce the number of precancerous lesions in a dimethylhydrazine (DMH)-induced rat colon cancer model (Smith et al., 1998). Lund and coworkers (2001) compared the ability of four isothiocyanates (ITC), benzyl-ITC, allyl-ITC



SCHEME G.27 Chemical structures of glucosinolates and their breakdown products following enzymic hydrolysis by myrosinase (Adapted from Pessina et al., *Arch. Biochem. Biophys.*, 280:383–389, 1990, by Steinkeller et al., *Mutat. Res.*, 480–481:285–287, 2001. With permission.)

(AITC), phenylethyl-ITC (PEITC), and methyl-sulphinylbutyl-ITC (sulforaphane), to induce apoptosis in colorectal adenocarcinoma cells (HT9). The relative potency of these compounds to reduce adherent cell number was BITC=AITC> PEITC>>sulforaphane. The primary action of these ITCs was to block rapidly proliferating cancer cells at G2/M. These researchers commented that reducing the levels of glucosinolates by breeding to reduce the hot and bitter flavors associated with their degradation products might impair the health benefits associated with these vegetables.

Glucosinolates are activators of liver-detoxification enzymes; their mode of protection appears to involve modulation of carcinogen metabolism by inducing phase II detoxification enzymes, while inhibiting phase I detoxification enzymes (Hecht, 1999). Shapiro et al. (1980) showed substantial amounts of isothiocyanates were converted to dithiocarbamates. Smith and coworkers (1998) observed that the purified glucosinolate,

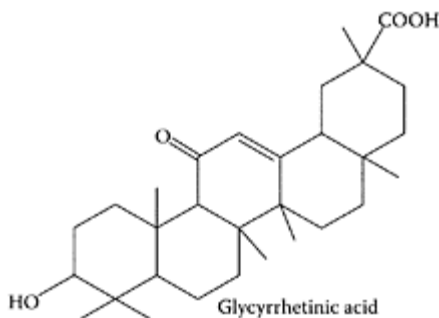
sinigrin, reduced the number of precancerous lesions in rat colon induced by dimethylhydrazine (DMH) and was associated with an increase in apoptosis within 48 hours of exposure to DMH. The underlying mechanism responsible for cell death induced by four isothiocyanates (ITCs), benzyl-ITC, allyl-ITC, phenylethyl-ITC, and methylsulphinylbutyl-ITC (sulforaphane), was studied by Lund et al. (2001). The primary mechanism involved blocking the rapidly proliferating colorectal adenocarcinoma (HT29) cancer cells in G2/M.

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Glycyrrhin and 18β-Glycyrrhetinic acid

Glycyrrhin, a pentacyclic triterpene derivative, is the main, water-soluble constituent of licorice roots (*Glycyrrhiza glabra* L.). Besides being a sweetening and flavoring agent in foods, glycyrrhin has been used in Asia and Europe for many years as an antidote, demulcent, and folk medicine. Glycyrrhin is hydrolyzed by the intestinal bacterial glucuronidase to the corresponding aglycone, 18β-glycyrrhetinic acid,



Glycyrrhetic acid. (From Wang et al., *J. Chromatogr. A.*, 811:219–224, 1998. With permission.)

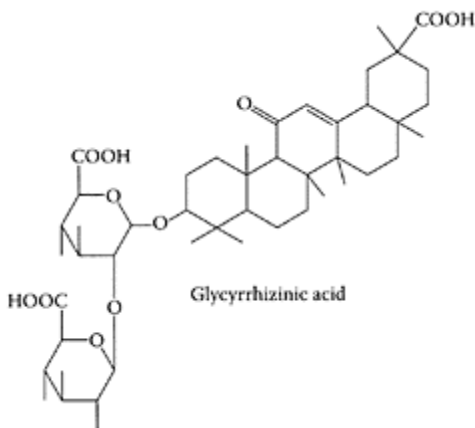
which is then absorbed by the body. Both glycyrrhin and its aglycone have been associated with a number of health benefits, including antiulcerative (Doll et al., 1962), anti-inflammatory (Ohuchi et al., 1981), antiviral (Ito et al., 1988), antihepatitis (Kiso et al., 1984), and antitumor (Suzuki et al., 1992) properties. Jeong and coworkers (2002) recently showed that the potent hepatoprotective properties of 18 β -glycyrrhetic acid were due to its ability to block bioactivation of carbon tetrachloride by inhibiting cytochrome P450 2E1 expression.

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Glycyrrhizic acid

Glycyrrhizic acid, another component of licorice root, was found to be active against a number of viruses, such as herpes simplex type 1, varicella-zoster virus, human cytomegalovirus, hepatitis A, B, and C viruses, human immunodeficiency virus-1, and influenza virus (Crance et al., 1994; Sato et al., 1996; Arase et al., 1997; Utsunomiya et al., 1997). Recently, Lin and coworkers (2003) showed glycyrrhizic acid inhibited the replication of the Epstein-Barr virus, which differed from



Glycyrrhizic acid. (From Wang et al., *J. Chromatogr. A.*, 811:219–224, 1998. With permission.)

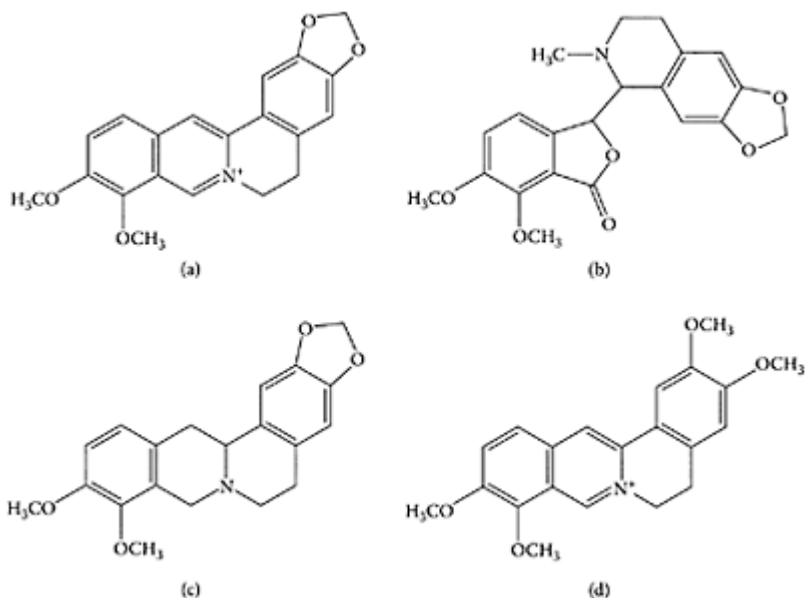
mode of action of nucleoside analogues, which inhibit DNA polymerase. The ability of glycyrrhizic acid to protect against aflatoxin-induced oxidative stress in hepatoma cells was recently reported by Chan and coworkers (2003).

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SCHEME G.28 Goldenseal isoquinoline alkalioids: berberine (a); hydrastine (b); canadine (c); palmatine (d). (From Weber et al., *J. Agric. Food Chem.*, 51:7352–7358, 2003. With permission.)

Goldenseal (*Hydrastis canadensis* L.)

Goldenseal (*Hydrastis canadensis* L.) is a perennial, herbaceous plant native to eastern North America. It is a medicinal herb used primarily for its antimicrobial properties (Diamond and Towers, 1999; Upton, 2001). Goldenseal is a very popular supplement and is often sold together with *Echinacea*. The dried roots or rhizome of goldenseal contain a number of isoquinoline alkaloids, the major ones being hydrastine and berberine, together with smaller amounts of canadine and palmatine (Scheme G.28). The American Herbal

Pharmacopoeia states that fresh or dried roots from goldenseal should not contain less than 2.5 percent berberine and 2.0 percent hydrastine, on a dry-weight basis (Upton, 2001). Berberine has been used to treat psoriasis and eye infections (Sabir et al., 1978; Muller et al., 1995).

Since goldenseal is used extensively in eyewashes and in skin lotions, Inbaraj and coworkers (2001) examined possible adverse interactions with light. In the presence of 50 μ M berberine, UVA irradiation of transformed epidermal human-cell line, HaCaT keratinocytes, resulted in a decrease in cell viability of 80 percent, while tripling the amount of DNA damage. Based on these results, avoiding sunlight or artificial-light sources emitting UVA was recommended when using preparations containing goldenseal or berberine. However, these researchers pointed out that antiseptic properties associated with such topical preparations could be due to such interactions.

Rehman et al. (1999) showed that both *Echinacea* and goldenseal enhanced antibody production in rats, each acting on a different immunoglobulin subtype. *Echinacea* treatment improved the IgG immune response in rats one or two weeks after treatment with KLH, a novel antigen, keyhole limpet hemocyanin, while goldenseal augmented IgM response during the first two weeks of treatment. Such augmentation in antibody response could lead to identification of novel immune adjuvants.

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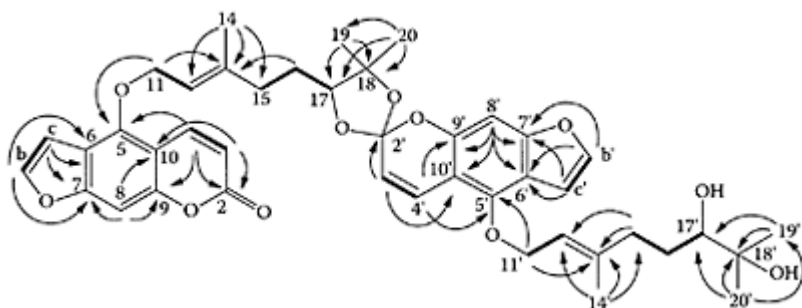
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Grapefruit

Grapefruit juice has been reported to interact and elevate the pharmacological efficacy of a number of medications, including cyclosporine (Ducharme et al., 1995), midazolam (Kupferschmidt et al., 1995), felodipine (Bailey et al., 1990), and lovastatin (Kantola et al., 1998). The bioavailability of these drugs was enhanced 1.5- to 15-fold following ingestion of grapefruit juice. The lipophilic nature of these drugs necessitates their oxidative transformation by cytochrome P450 (CYP3A4) prior to excretion. The major flavonoid in grapefruit is naringin, which, together with its aglycone naringenin, both inhibit CYP3A4, although naringenin was found to be the more potent inhibitor *in vitro* (Miniscalco et al., 1992). However, Schmiedlin-Ren et al. (1997) reported that the furanocoumarin derivative, dihydroxybergapten, was a far more potent inhibitor, which was later shown to have a very low IC₄₀ (Ho et al., 1998). The marked differences between the levels of naringin, naringenin, and bergapten (5-methoxypsoralen) in grapefruit and grapefruit-juice products were attributed by Ho et al. (2000) to the contradictory drug-interaction results reported in the literature. Tassaneeyakul et al. (2000) showed that, in addition to the human microsomal CYP3A4, CYP2C19 was also inhibited by grapefruit extract or its isolated furanocoumarins. Using the carageenan-induced paw oedema model, Mahgoub (2001) also reported grapefruit juice potentiated the effects of the nonsteroidal, anti-inflammatory drug diclofenac to inhibit other cytochrome P450 isoenzymes. A new CYP3A4 inhibitor, a furanocoumarin derivative, paradisin C, was recently identified by Ohta and coworkers (2002) in grapefruit juice (Scheme G.29).

In vitro studies by Goff-Klein et al. (2003) on human liver microsomes and rat hepatocytes and microsomes showed interspecies differences involved different CYP450 isoenzymes in the metabolism of simvastatin (SV), a drug used to treat hypercholesterolemia, in the presence of bergamottin, a grapefruit component. Inhibition of CYP450 isoenzymes by bergamottin can lead to prolonged exposure to SV with high serum simvastatin concentrations, increasing the risk of skeletal-muscle toxicity (Bogman et al., 2001). Prolonged exposure to some drugs may be beneficial, while drugs, such as simvastatin, could be harmful. As a result, grapefruit is no longer served in hospitals.

Miyata et al. (2002) examined the effect of grapefruit juice on the heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), a component in cooked meat and fish implicated in the etiology of colon cancer. They showed that pretreatment of rats with grapefruit juice suppressed colon DNA damage using the comet assay. A 6.2-fold and 5.4-fold increase in migration of DNA and frequency of tailed nuclei were observed in colon nuclei of PhIP-treated rats compared to vehicle-treated rats (Figure G.45). In contrast, a reduction of



SCHEME G.29 COSY (bold lines) and HMC (arrows) NMR Spectral data correlations observed for paradisin C. (From Ohta et al, *Tetrahedron*, 58:6631–6635, 2002. With permission.)

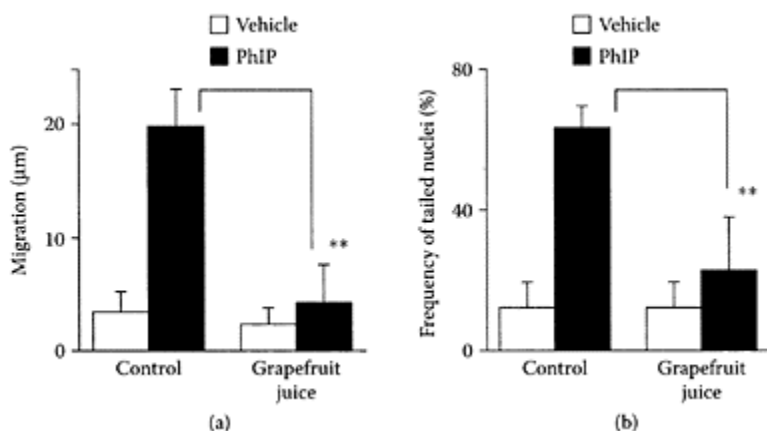


FIGURE G.45 Effect of pretreatment with grapefruit juice on PhIP-induced DNA damage in rat colon, (a) Migration, (b) Frequency of tailed nuclei. Rats had free access to grapefruit juice five days prior to administration of PhIP (60 mg/kg). Colon nuclei were isolated 3 h after PhIP treatment. Migration measured as the difference between the length of

the whole comet and the diameter of the head. Values represent the mean \pm SD ($n=3$ in each group). $**p<0.01$, significant differences from corresponding control group. (From Miyata et al., *Cancer Lett.*, 183:17–22, 2002. With permission.)

20 percent and 36 percent in DNA migration and frequency of tailed nuclei was evident in grapefruit juice-treated rats compared to the control rats, respectively.

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Grape juice

Grapes are one of the richest sources of phenolic compounds compared to other fruit (Machiex et al., 1990). They contribute flavonoids and polyphenolic tannins, in addition to nonflavonoid hydroxy-cinnamic acids, hydroxybenzoic acids, and stilbene. Many of these compounds were found to be potent antioxidants inhibiting the *in vitro* oxidation of LDL cholesterol. Frankel and coworkers (1998) found the commercial Concord and blends of grape juices had comparable inhibitory activity to that of red wine, with respect to the *in vitro* oxidation of human low-density lipoproteins. Using a hamster model of atherosclerosis, Vinson et al. (2001) showed grape juice was twice as effective in lowering cholesterol compared to dealcoholized wine or red wine, two to six times more effective in decreasing LDL, and twice as effective as red wine in preventing atherosclerosis (Figure G.46). Grape juice was a more efficient *ex vivo* antioxidant, as it was more effective in increasing the lag time by four times compared to either dealcoholized wine or red wine. Park et al. (2003) showed grape juice reduced total free-radical levels and DNA damage in 67 healthy Koreans (16 women and 51 men) maintained on a daily grape-juice regime of 480 mL pure grape juice twice a day for eight weeks. The results from this study combined, with antiplatelet and antioxidant benefits reported previously for grape consumption (O’Byrne et al., 2002; Vinson et al., 2000), suggests grape juice should become a regular part of a healthy diet.

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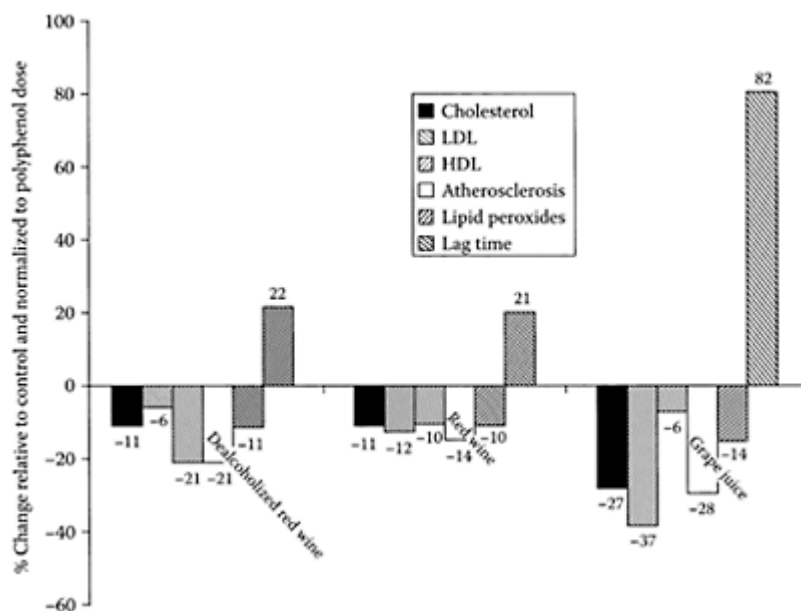


FIGURE G.46 Comparative polyphenol efficiency of beverages with respect to atherosclerosis, lipid, and antioxidant parameters. (Vinson et al., *Atherosclerosis*, 156:67–72, 2003. With permission.)

Grape seeds

Grape-seed extract is widely consumed in the United States as a dietary supplement because of a number of related health benefits associated with its bioflavonoids or procyanidins. Zhao et al. (1999) showed that a polyphenolic fraction from grape seeds exhibited antitumor-promoting activity by reducing tumor incidence in a 7,12-dimethylbenz-*a*/anthracene (DMBA)-initiated and 12-*O*-tetradecanoylphorbol 13 acetate (TPA)-promoted SENCAR mouse skin two-stage carcinogenesis model system. The antitumor-promoting activity was attributed to the potent antioxidant properties of the grape-seed polyphenols. Procyanidin B5–3' gallate was identified with the most potent antioxidant activity and potential as a cancer chemopreventive and anticarcinogenic agent. Agarwal and coworkers (2000) also showed grape-seed extract inhibited growth and induced apoptosis in human prostate-cancer cells, both in culture

and in nude mice. These researchers (Agawal et al., 2002) found grape seed extract induced apoptosis in human prostate carcinoma DU145 cells by activation of caspases.

Yamakoshi and coworkers (1999) showed that feeding a proanthocyanidin-rich grape seed extract to cholesterol-fed rabbits significantly reduced severe atherosclerosis in the aorta. It decreased the number of oxidized LDL-positive, macrophage-derived foam cells in atherosclerotic lesions in the aorta of cholesterol-fed rabbits, as a result of its ability to trap reactive-oxygen species in aqueous solution. Shao et al. (2003) confirmed the cardioprotective activity of grape seed proanthocyanidin by its ability to attenuate oxidant injury in chick embryonic ventricular myocytes. The molecular mechanisms involved in cardioprotection by a novel grape seed proanthocyanidin extract (IH636) were shown by Bagchi et al. (2003) to include:

- potent hydroxyl and other free-radical scavenging activities
- antiapoptotic, antinecrotic, and antiendonucleolytic potentials
- modulation of apoptotic regulators, *bcl-X_L*, p53, and *c-myc* genes
- inhibition of cytochrome P450 2E1
- inhibition of adhesion molecules
- modulation of proapoptotic and cardioregulatory genes, *c-JUN*, *JNK-1*, and *CD36*.

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Green tea

Green tea, a popular beverage in Japan made from the leaves of *Camellia sinensis*, is recognized for its health benefits. It is a nonfermented product obtained by leaf dessication that contains potent, polyphenolic antioxidants, with a flavan-3-olic structure, referred to as green-tea catechins. They include seven types, (-)-gallocatechin (GC), (-)-epigallocatechin (EGC), (+)-catechin (C), (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EC), (-)-gallocatechingallate (GCG), and (-) epicatechingallate (ECG) (Bonoli et al., 2003).

Many studies have shown that drinking EGCG and green tea prevents carcinogenesis in rodent organs (Wang et al., 1992; Fujiki, 2002). Kavanagh et al. (2001) showed green tea had a significant chemoprotective effect against 7, 12-dimethyl(a)anthracene (DMBA)-induced mammary tumorigenesis in Sprague-Dawley rats. Inhibition of human breast cancer Hs578T cell proliferation by green tea appeared to be mediated, in part, by induction of p27^{Kip} cyclindependent kinase inhibitor (CKI) expression. Gupta et al. (2002) summarized the antimutagenic and anticlastogenic properties of green and black teas. Green tea inhibited mutagenesis at concentration levels equivalent to human daily consumption. Using human umbilicalvein endothelial cells, Kojima-Yuasa et al. (2003) demonstrated, for the first time, that green-tea extracts reduced expression of vascular endothelial growth factor (VEGF) receptors fms-like tyrosine kinase (Flt-1) and fetal liver kinase-1/Kinase insert domain containing receptor (Flk-1/KDR). The antiangiogenic property of green-tea extracts has therapeutic potential in preventing the development of new microvascular networks (angiogenesis) needed for tumor growth. Maiti and coworkers (2003) also found green-tea polyphenols inhibited angiogenesis by reducing vascularization of chicken chorioallantoic membrane (CAM) by an angiogenin-like protein isolated from goat serum. Kemberling et al. (2003) showed greentea EGCG effectively inhibited bladder-tumor implantation growth in a Fischer 344 rat model, pointing to its potential as an intravesical chemotherapeutic agent.

Reducing the risk of coronary artery disease is associated with a number of factors, including inhibition of platelet function. EGCG was reported to inhibit platelet aggregation, possibly by involving inhibition of cytoplasmic calcium increase (Kang et al., 1999). Lill and coworkers (2003) found that only those green catechins with a galloyl group in the 3' position inhibited platelet aggregation, while those without a galloyl group (catechin and epicatechin) or with

TABLE G.36

The Antiviral Effect of EGCG and Green Tea

Agent	IC ₅₀ (μM)	
	Inactivation of Adenovirus	Effect on Infectious Virus Production
Epigallocatechin gallate (EGCG)	250	25

Green tea infusions ^a (GT-20)		
Gunpowder	245	34
Uncle Lee's	2840	N.D.
Celestial Seasonings	3095	45
Tetley	490	45

^a Expressed in terms of estimated EGCG concentration in the tea.

Source: From Weber et al., *Antiviral Res.*, 58:167–173, 2003. With permission.

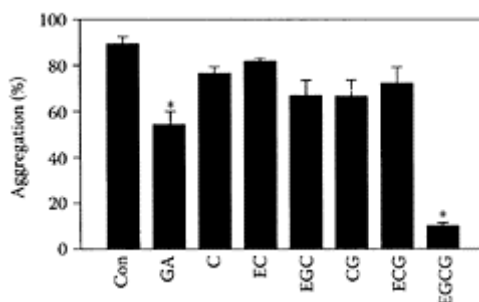


FIGURE G.47 Effect of various green-tea catechins (100 $\mu\text{mol/L}$) on thrombin-induced platelet aggregation (means \pm S.E.M., $n=5$, $*p<0.05$ versus control). (From Lill et al., *FEBS Lett.*, 546:265–270, 2003. With permission.)

the galloyl group in the 2' position (epigallo-catechin) did not. EGCG proved to be the most effective in reducing thrombin-induced aggregation of washed human platelets (Figure G.47).

The ability of green-tea catechins to inhibit adenovirus infection and adenain, the human adenovirus 2 endopeptidase, was reported by Weber and coworkers (2003). EGCG proved the most potent inhibitor of four green-tea catechins tested with a IC_{50} of 200 μM (Table G.36). Since the viral protease, adenain, appeared to be the target of EGCG, it is possible that all adenoviruses are sensitive to its action.

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Guava

Guava (*Psidium guajava* L.) is an evergreen native to Mexico and Cenral American countries. Guava leaves, roots, and fruits have been used to prevent and treat diarrhea (Lutterodt, 1989) and diabetes (Cheng and Yang, 1983). Studies have also reported that guava has antimutagenic activity, including the identification of (+)-galloocatechin, an antimutagenic compound in guava leaves (Grover and Bala, 1993; Matsuo et al., 1993). Popular Mexican medicine recommends the use of guava leaf water decoction to treat acute diarrhea, colic, flatulence, and gastric pain (Aguilar et al., 1994). Arima and Danno (2002) recently isolated four antibacterial compounds in guava leaves. In addition to guajavarin and quercetin, two new flavonoid glycosides were characterized. The latter were identified as morin-3-*O*- α -L-lyxopyranoside and morin-3-*O*- α -L-arabopyranoside, both of which were effective against *Salmonella enteritidis* and *Bacillus cereus*. Flavonoids, such as quercetin, are also associated with spasmolytic effect and antidiarrheic capacity of guava-leaf products. Lozoya and coworkers (2002) conducted a randomized, double-blinded clinical study that established the safety and efficacy of a phytodrug made from guava leaves standardized in its quercetin content. Decreased

abdominal pain was experienced by adult patients suffering from acute diarrheic disease after taking a capsule containing 500 mg of the product every eight hours for three days. The research ers suggested it could be a useful alternative as an antispasmodic product.

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Gum acacia

see **Acacia gum**

Guar gum

Guar gum, a soluble fiber extracted from the endosperm of the Indian cluster bean (*Cyanopsis tetragonoloba* L.), is a summer legume grown mainly in Western India and Eastern Pakistan. It is a nongelling gum similar to locust-bean gum used extensively in the food industry. Guar gum is a galactomannan in which the molar ratio of galactose to mannose is approximately 1:2. Viscous fibers are very effective for glycemic control (Jenkins et al., 1979; Wolever et al., 1979; Wursch and PiSunyer, 1997). Thus, guar gum, a viscous fiber, is considered to be effective as long as it is not hydrolyzed (Cabre, 2004). A partially hydrolyzed guar gum was shown by Slavin and Greenberg (2003) to have a

number of clinical uses, including reducing the incidence of diarrhea in septic patients maintained on enteral nutrition, reducing symptoms of irritable-bowel syndrome, and increasing bifidobacterium in the gut.

Early studies by Jenkins et al. (1979) suggested guar gum could lower total plasma total cholesterol and LDL cholesterol. Castro and coworkers (2003), however, were unable to find any changes in serum lipids of hypocholesterolemic rats maintained on a diet containing 1.5 percent of several hydrocolloids, including guar gum.

The suggestion that guar gum may be beneficial for reducing weight is attributed to increasing viscosity of the bowel contents and the feeling of postprandial satiety (Blackburn et al., 1984; Van de Ven et al., 1994). Based on a number of clinical trials, guar gum is recommended for treating obese patients. Pittler and Ernst (2001) conducted a meta-analysis of randomized trials in which dietary guar gum was used for reducing body weight. Based on their findings they could not recommend guar gum as a treatment for reducing body weight.

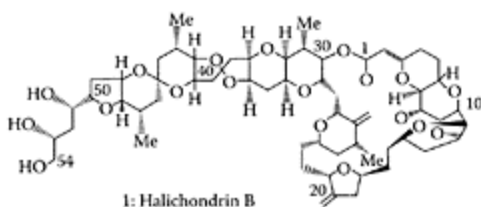
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H

Halichondrin B

Halichondrin B, a poly ether macrolide isolated from marine sponges and tunicates, was shown to have potent cytotoxicity properties *in vitro* and anticancer properties *in vivo* (Hirata and Uemura, 1986; Litaudon et al., 1994; Fodstad et al., 1996). The sponge *Lissodendoryx* n. sp. 1 was the most promising



Halichondrin B. (From Seletsky et al., *Bioorg. Med. Chem. Lett.*, 14:5547–5550, 2004. With permission.)

source of halichondrin B components, although it is found in four other sponges. The potential of halichondrin B as an anticancer drug (Pettit et al., 1993a) is limited by its relative scarcity. Halichondrin B disrupts mitotic spindle formation and induces mitotic arrest by inhibiting tubulin assembly and microtubule assembly (Pettit et al., 1993b). A synthetic C(1)–C(38) halichondrin subunit was reported to exhibit anticancer properties similar to that of halichondrin B (Stamos et al., 1997; Towle et al., 2001). Wang et al. (2000) synthesized simplified analogues of halichondrin B that still retained cell growth inhibitory potency *in vitro*. Austad and coworkers (2002) synthesized C(37)–C(54) halichondrin subunits. The National Cancer Institute selected halichondrin B for drug development.

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Hawthorn

Hawthorn (*Crataegus*) grows in the northern temperate regions of the world, mainly in East Asia, Europe, and North America. The bright-red berries of hawthorn fruit contain fructose, flavonoids, proanthocyanidins, triterpenes, organic acids, vitamins, and minerals (Huang, 1993). Zhang et al. (2001) reported hawthorn fruit was rich in phenolic antioxidants, particularly hyperoside, isoquercitrin, epicatechin, chlorogenic acid, quercetin, rutin, and protocatechuic acid. The ability of hawthorn fruit to lower total serum cholesterol, LDL cholesterol, and triglycerides in hyperlipidemic individuals was reported by Chen and coworkers (1995). More recent studies by Zhang et al. (2002a) showed inclusion of a 0.5 percent aqueous ethanolic extract from hawthorn-fruit powder in a semisynthetic diet containing 0.1 percent cholesterol diet to rabbits lowered serum total cholesterol and triacylglycerols by 10 percent and 13 percent, respectively (Figure H.48). A possible mechanism involved greater bile-acid excretion mediated by upregulation of hepatic cholesterol 7 α -hydroxylase and inhibition of cholesterol

adsorption mediated by downregulation of intestinal acyl Co A: cholesterol acyltransferase activity.

Pittler et al. (2003) examined the efficacy of hawthorn extract in treating chronic heart failure by meta-analysis of randomized trials. Their results suggested a significant benefit was derived from hawthorn extract as an adjunctive treatment for chronic heart failure. A pilot study conducted by Walker and coworkers (2002) using 36 mildly hypertensive subjects found hawthorn extract reduced the diastolic blood pressure in 10 out of the 19 subjects, with a trend in the reduction of anxiety. The small number of subjects and the low levels of hawthorn extract used in this study, however, warrants further investigation.

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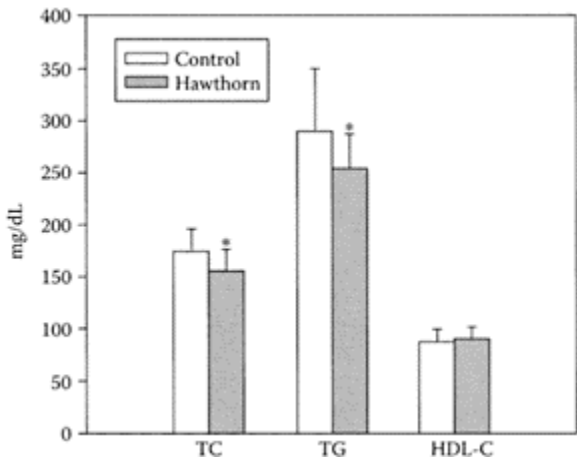


FIGURE H.48 Effects of supplementation of 0.5 percent hawthorn fruit ethanolic extract (equal to 2 percent dried-fruit powder) in diet on serum total cholesterol (TC), triacylglycerols (TG), and high-density lipoprotein cholesterol (HDL-C) in hamsters. Values are means±S.D., n=15. *Differs significantly at p<0.05

(From Zhang et al., *Food Res. Inter.*, 35:885–891, 2002a. With permission.)

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Hemp

The annual herbaceous plant hemp (*Cannabis saliva* L.) has been traditionally grown for its fiber and oil. Its seeds were reported to have a number of health benefits, including lowering cholesterol and high blood pressure (Jones, 1995). Hemp-seed oil is perfectly balanced with respect to the ratio (3:1) of the two essential polyunsaturated fatty acids, linoleic to linolenic acid. The presence of γ -linolenic acid in hemp oil makes it an excellent ingredient in light body oils and lipid-enriched creams (Rausch, 1995).

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Herbs

see also Individual herbs Herbs are used extensively and with increasing interest in North America in complimentary and alternative medicines (Eisenberg et al., 1998). Women (particularly white, middle-aged women) appear to be the major users of these nontraditional therapies (Astin, 1998; Druss and Rosenheck, 1999). Like pharmaceutical drugs, herbal medicines can be therapeutic at one dose and toxic at another (Fugh-

Berman, 2001). Of particular concern, however, are the possible adverse effects of herbal-drug interactions. In a review of herbs commonly used by women, Tesch (2001) noted that some herbs, such as *Ginkgo biloba*, were more effective than the placebo for dementia. However, when taken with aspirin or warfarin, it inhibited the platelet-activating factor and was associated with serious bleeding. St. John's Wort, shown to be effective for treating mild to moderate depression in the short term, suffers from many drug interactions. Ginseng may attenuate postprandial glycemia and improve psychological symptoms in perimenopausal women. A decrease in certain cancers associated with ginseng, however, is offset by its impurity and possible side effects. A review of herbal medicines and epilepsy by Spinella (2001) noted that certain herbal sedatives (kava kava, valerian, chamomile, passion flower) may potentiate the effects of antiepileptic medications, increasing their sedative and cognitive effects. However, limited evidence suggests that many of these herbal medicines, particularly those containing ephedrine and caffeine, can exacerbate seizures. A list of the clinical reports for some herb-drug interactions is summarized in Table H.37. A review of alternative medicines for treating glaucoma by Rhee et al. (2001) indicated that while *Ginkgo biloba* and other Chinese herbal medicines do not affect intraocular pressure, they may have a beneficial effect by improving blood flow to the optic nerve. These researchers cautioned that using some herbal medicines could have possible toxicities and side effects.

Zou et al. (2002) examined the *in vitro* effects of 25 purified components from commonly used herbal products on the catalytic activity of cDNA-expressed cytochrome P450 isoforms. Herbal products containing kava kava, *Ginkgo biloba*, garlic, or St. John's Wort were capable of inhibiting the metabolism of coadministered medications in which the primary elimination route was via cytochrome

TABLE H.37

Clinical Reports of Selected Herb-Drug Interactions	
Herb and Drug(s)	Results of Interaction
Ginkgo (<i>Ginkgo biloba</i>)	
Apirin	Serious hyphema
Warfarin	Intracerebral hemorrhage
Thiazide diuretic	Hypertension
Ginseng (<i>Panax spp.</i>)	
Warfarin	Decreased INR
Phenelzine	Headache and tremor
Alcohol	Increased alcohol clearance
St. John's Wort (<i>Hypericum perforatum</i>)	
Paroxetine	Lethargy/incoherence
Setraline	Mild serotonin syndrome
Combined oral contraceptive	Breakthrough bleeding

(ethyloestradiol and desogestrel)

Valerian (*Valeriana officinalis*)

Alcohol

A mixture of valepotriates reduces adverse effect of alcohol on concentration

Source: Adapted from Fugh-Berman, *Lancet*, 355:134–138, 2001.

P450. Constituents in these herbal products inhibited one or more of the cytochrome P450 isoforms at concentrations less than 10 μ M. Of the three main isoforms (CYP2C9, CYP2C19, and CYP3A4) affected, CYP2C19 proved to be the most sensitive. These herbal components were capable of eliciting clinically significant drug interactions.

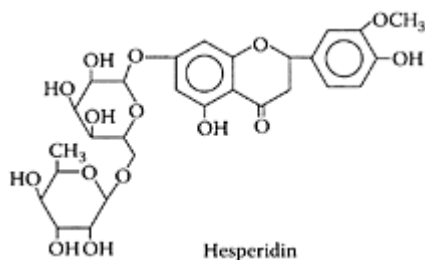
For a more detailed discussion of the risks associated with herbal medicines, the review articles by Izzo et al. (2004) and Zhou et al. (2004) are strongly recommended.

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Hesperidin

Hesperidin (3',5,7-trihydroxy-4'-methoxyflavonone-7-rhamnoglucoside), is a naturally occurring bioflavonoid present in fruits and vegetables. As a component of citrusfruit peel, it was shown to lower cholesterol in rats (Bok et al., 1999; Galati et al, 1994), as well as exhibit antioxidant activity *in vitro* (Van Acker et al., 1996; Chan et al., 1999).



(Adapted from Kanaze et al., *J. Pharm. Biomed. Anal.*, 36:175–181, 2004.)

A number of studies have shown dietary hesperidin, alone or in combination with diosmon, exerted anticarcinogenic effects in tongue, colon, esophageal, and urinary-bladder carcinogenic rat models (Tanaka et al., 1997a, b, 2000; Yang et al., 1997). In addition, hesperidin was also shown to have anti-inflammatory activity in mouse skin exposed to a tumor promoter (Koyuncu et al., 1999). Using the rat model for testing arthritis, Guardia and coworkers (2001) showed hesperidin inhibited both acute and chronic phases of inflammation. Sakata et al. (2003) examined the modulating effects of hesperidin on the expression and activity of COX-2 and iNOS enzymes induced by the endotoxin lipopolysaccharide (LPS). COX-2 and iNOS are inducible enzymes, which, in association with inflammatory responses, play a key role in carcinogenesis. Using mouse macrophage cells, hesperidin dramatically suppressed prostaglandin E₂, nitric dioxide, and expression of iNOS protein, which could explain its anti-inflammatory and antimutagenic properties (Figure H.49).

Hesperidin and 6-methylapigenin were reported by Marder et al. (2003) as new *Valeriana* flavonoids with activity on the central nervous system. 2*S*(-)-hesperidin was found to have sedative and sleep-enhancing properties potentiated by 6-methylapigenin. The chemistry and pharmacology of the citrus bioflavonoid hesperidin were reviewed by Garg et al. (2001).

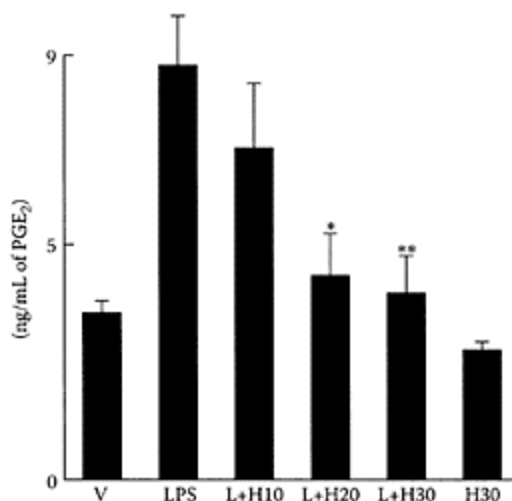


FIGURE H.49 PGE₂ production in RAW 264.7 cells. PGE₂ over production was induced by LPS (0.2 µg/mL medium, *L*) and suppressed by hesperidin (H), with various concentrations, *v*, cells treated with vehicle. *L+H10–L+H30*, cells treated with LPS and 10, 20, and 30 µM of hesperidin. H30 cells treated with hesperidin 30 µM. Mean PGE₂ concentration±SD of three separate experiments. **p*<0.005 and ***p*<0.003 compared with *L* by Student's *t*-test. (From Sakata et al, *Cancer Lett.*, 199:139–145, 2003. With permission.)

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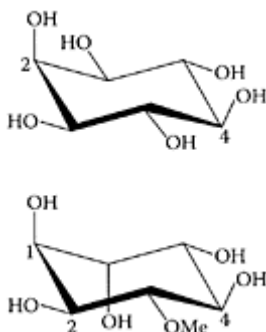
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High-density lipoproteins

see Lipoproteins

Honey

Honey, a complex mixture of carbohydrates, has been studied extensively (Horvath and Molnarl-Perl, 1998; Gomez Barez et al., 2000). In addition, some cyclitols or poly alcohols, such as myo-inositol and mannitol, have also been reported in edible honeys (Horvath and Molnarl-Perl, 1998). Sanz and coworkers



Myo-inositol and D-pinitol. (From Hart et al., *Carbohydr. Res.*, 339:1857–1871, 2004. With permission.)

TABLE H.38

Anti-inflammatory Effect of (+)-Pinitol on Carrageenan-Induced Paw Edema in Rats¹

Treatment	Dose (mg/kg, i.p.)	Edema Volume (mL)	Inhibition (percent)
Control (saline, 3.0 mL/kg, i.p.)		0.90±0.02	—
Phenylbutazone	100	0.23±0.01*	74.44
(+)-Pinitol	2.5	0.53±0.04*	41.11
	5	0.44±0.02*	51.11
	10	0.31±0.02*	65.55

¹Values are mean±S.E. (n=6).

**p*<0.001 versus control; Student's t-test.

From Singh et al., *Fitoterapia*, 72:168–170, 2001. With permission.

(2004) identified quercitol, pinitol, 1-*O*-methylmuco-inositol, and muco-inositol for the first time in edible honey. Of 28 honeys examined, most had myo-inositol and pinitol, while only in some samples were the other cyclitols detected. The anti-inflammatory nature of (+)-pinitol, isolated from *Abies pindrow* leaves, was demonstrated by Singh and

coworkers (2001) using the carrageenan-induced paw edema in rats. A significant reduction in edema volume was evident in the presence of pinitol with a dose of 10 mg/kg comparable to that of phenylbutazone (Table H.38).

Certain honeys derived from such floral sources as *Leptospermum scoparium* (Manuka) and *L. polygalifolium* (Meadhoney) provide additional antioxidants, antibacterial agents, and other unidentified compounds and are referred to as therapeutic honeys (Lusby et al., 2002). The ability of these honeys to prevent microbial growth in the moist-wound environment accounts, in part, for their beneficial effects in wound healing. Tonks et al. (2003) examined the wound-healing ability of three honeys (manuka, pasture, and jelly bush) on the activation state of immunoincompetent cells, using the human monocytic cell-line model MonoMac-6. All of the honeys significantly increased the release of important inflammatory cytokines TNF- α , IL-1 β , and IL-6 (Figure H.50). These cytokines are both proinflammatory and anti-inflammatory. While all three honeys showed significant increases in cytokines compared to the sugar-solution control, the

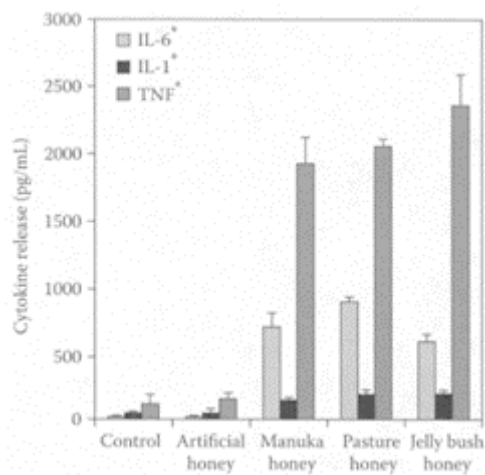


FIGURE H.50 Effect of 1 percent (w/v) honeys on TNF- α , IL-1 β , and IL-6 release from isolated human peripheral-blood monocytes. Results are expressed as mean \pm SD. * p <0.001 analyzed by ANOVA and Tukey's pair-wise comparisons. (From Tonks et al., *Cytokine*, 21:242–247, 2003. With permission.)

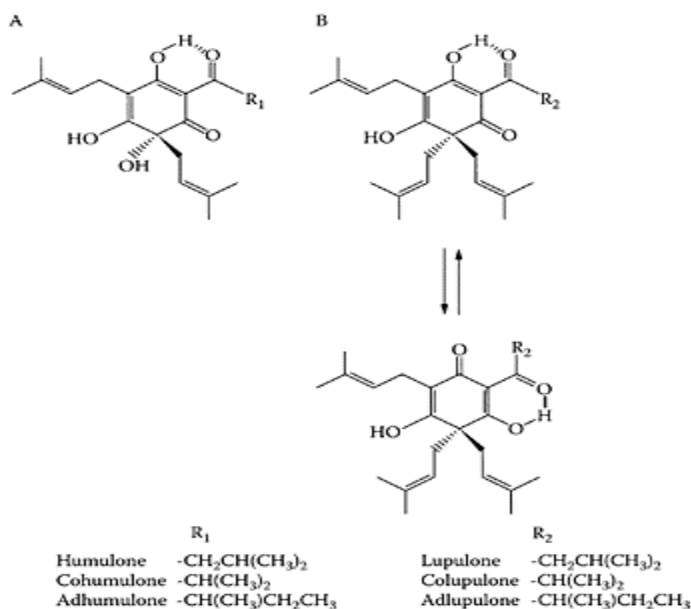
Australian jelly-bush honey had the greatest effect. The ability of these honeys to regulate the production of cytokines is probably due to the presence of components other than sugar. These components have yet to be identified but could involve cyclitols.

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Hops (*Humulus lupulus* L.)

The bitter taste and aroma of beers is due to the bitter acids extracted from hops added to the sweet wort during brewing. These are composed of α - and β -acids, humulone, cohumulone, adhumulone, lupulone, colupulone, and adlupulone and their oxidation products (Scheme H.30) (Verzele and Potter, 1978). The potential of bitter acids, such as humulone, as chemotherapeutic or chemopreventive agents was evident by their ability to inhibit angiogenesis (Shimamura et al., 2001), suppress cyclooxygenase-2 transcription (Yamamoto et al., 2000), induce differentiation of



SCHEME H.30 Chemical structures of hop bitter acids: (A) α -acids; (B) β -acids. (From Chen and Lin, *J. Agric. Food Chem.*, 52:55–64, 2004. With permission.)

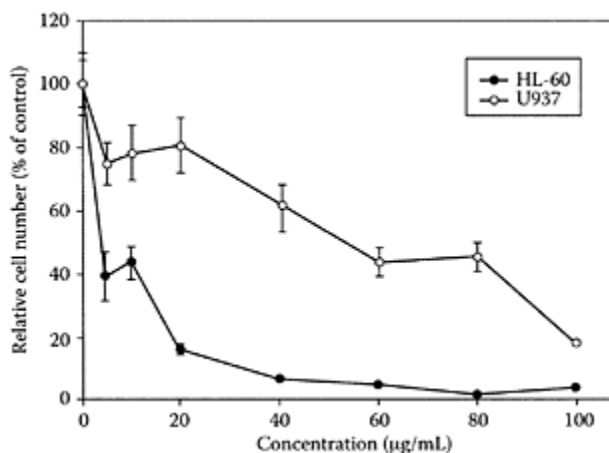


FIGURE H.51 Effect of hop bitter acids on cell viability, HL-60 and U937 cells when treated with either 5

μL/mL of DMSO as vehicle control or various concentrations of hop bitter acids for 24 h. Cell viability was determined by luminescent ATP detection assay kit, with data representing the means ± of three determinations. (From Chen and Lin, *J. Agric. Food Chem.*, 52:55–64, 2004. With permission.)

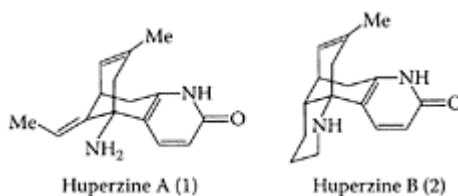
myelogenous leukemia cells (Honma et al., 1998), inhibit tumor promotion by 12-*O*-tetradecanoyl-phorbol-13-acetate (Yasukawa et al., 1995), and induce apoptosis in human leukemia HL-60 cells (Tobe et al., 1997). Chen and Lin (2004) attempted to delineate the mechanism whereby hop bitter acids triggered apoptosis in human leukemia-cell lines HL-60 and U937. The hop bitter acids inhibited HL-60 cell viability in a dose-dependent manner, with an IC₅₀ of 8.67 μg/mL (Figure H.51). The U937 cells proved much more resistant to the action of the hop bitter acids with an IC₅₀ value of around 58.87 μg/mL. Several mechanisms were proposed for triggering apoptosis involving Fas activation and mitochondrial dysfunction.

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Huperzine A and B

Huperzine A (HupA), a sesquiterpene alkaloid obtained from Chinese club moss (*Huperzia serrata*) or *Lycopodium serrata*, has been used as the folk medicine *Quian Ceng Ta* for centuries (Liu et al., 1986). It is a potent, highly specific, and reversible inhibitor of acetylcholinesterase, equivalent or superior to physostigmine, galanthamine, donepezil, and tacrine, approved drugs for treating



(From Lee et al., *Tetrahedron Lett.*, 45:285–287, 2004. With permission.)

Alzheimer's disease that are capable of crossing the blood-brain barrier (Wang et al., 1986; Wang and Tang, 1998). As a promising therapeutic agent for treating Alzheimer's disease, Wang et al. (2000) showed that huperzine A decreased the incidence rate of vascular dementia via multiple mechanisms involving the cholinergic system, oxygen free radicals, and energy metabolism. This was evident by its ability to significantly restore choline acetyl transferase activity in the hippocampus of rats, as well as reducing superoxide dismutase, lipid peroxide, lactate, and glucose to normal levels (Table H.39). Zhao and Tang (2002) showed huperzine A preferentially inhibited the tetrameric molecular form of acetylcholin-esterase in the cerebral cortex, hippocampus, and striatum of the rat brain, while tacrine and rivastigine preferentially inhibited the monomeric form. Physostigmine showed no form selectivity in any brain region. Donepezil varied from region to region with respect to its preferential inhibition of either the G4- and G1 selectivity. The different inhibitory preferences among acetylcholinesterase inhibitors require further study in relation to their effect on Alzheimer's disease. To understand the molecular events leading to Alzheimer's disease, Zhang and Tang (2003) examined the effect of huperzine A on staurosporine neuronal apoptosis in primary cultured rat cortical neurons. They demonstrated for the first time that huperzine A attenuated neurotoxin staurosporine-induced apoptosis, possibly via upregulation of bcl-2, downregulation of bax, and reduction in immunoreactive caspase-3 proenzyme.

The potential of huperzine A as a therapeutic agent for Alzheimer's disease was demonstrated by Zhang et al. (2004), who showed it increased the downregulation of secretory amyloid proteins by upregulating protein kinase C on infused rats and human embryonic kidney 293 Swedish mutant cells.

Tonduli and coworkers (2002) found huperzine A was extremely effective in preventing epileptic activity induced in rats by soman. Its ability to prevent toxicity was due to its protection of the enzyme acetylcholinesterase and reduction of hypercholinergy by soman at the electrophysiological level.

Huperzine B, a cogener of huperzine A in club moss, was reported to have a lower acetylcholinesterase inhibitory potency (Hu and Tang, 1987). Pretreatment of a rat pheochromocytoma cell line PC12 with huperzine B by

TABLE H.39

Effects of Huperzine A (HupA) on Superoxide Dismutase Activities and Lipid Peroxides in Rats Hypoperfused After Bilateral Ligation of the Common Carotid Arteries¹

Group	Superoxide Dismutase (nU/mg protein)			Lipid Peroxidase (nmol/mg protein)		
	Cortex	Hippocampus	Striatum	Cortex	Hippocampus	Striatum
Sham-operated	40.1±1.5**	46.3±1.9**	46.2±2.6**	2.69±0.07**	2.88±0.10**	3.55±0.17**
Saline-operated	69.0±2.9	74.8±6.0	97.3±5.7	3.70±0.14	4.11±0.17	5.38±0.27
HupA-treated ⁵ (0.1 mg/kg)	36.3±1.7**	43.0±2.0**	42.1±1.8**	2.80±0.07**	3.08±0.13**	3.36±0.07**

¹Rats were killed 40 min. after the last administration of huperzine A on day 33 following bilateral ligation of the common carotid arteries. From day 15 to day 33, huperzine A was administered orally twice per day. ***p*<0.01 versus saline-treated group.

Source: From Wang et al., *Bioorg. Med. Chem. Lett.*, 10:1029–1032, 2000. With permission.

Zhang and Tang (2000) showed it had similar neuroprotective effects to huperzine A against H₂O₂-induced injury. This neuroprotective effect could have application in the treatment of Alzheimer’s disease.

Three new *Lycopodium* alkaloids were recently identified by Tan et al. (2003) in *Huperzia serrata* as huperzine S (2β, 13β-epoxyalopecuridine), huperzine T (5α-hydroxy-6-oxodihydro-phlegmariu- rine A), and huperzine U (2,3-dihydro-12-hydroxyhuperzine B). The potential health benefits of these alkaloids still remain to be established.

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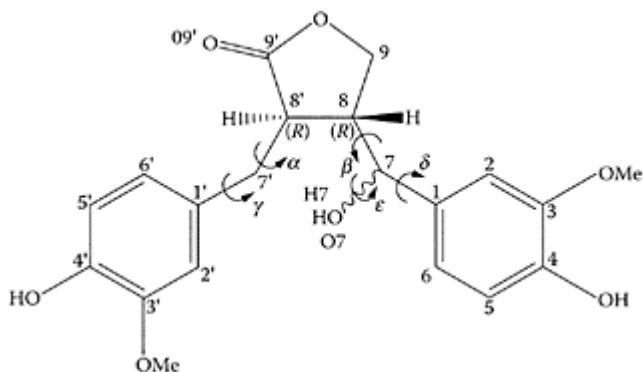
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Hydratis canadensis

see Golden seal

Hydroxymatairesinol

Hydroxymatairesinol (HMR) found in Norway spruce (Ekman, 1976), is related to matairesinol, an abundant



Hydroxymatairesinol. (From Taskinen et al., *J. Mol. Struct.*, (Theochem), 677:113–124, 2004. With permission.)

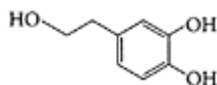
lignan found in rye bran. Its structure shown below consists of two guaiacol (2-methoxyphenol) units bonded to α and β positions of a γ -butyrolactone (2-oxacyclopentanone) ring via carbon atoms (Taskinen et al., 2004). Using Apc^{min} (adenomatous polyposis coli) mice, a genetically manipulated animal colon-cancer model, Oikarinen et al. (2000) found significantly lower numbers of adenomas in the small intestine of animals fed HMR compared to the other diets, including rye bran.

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Hydroxytyrosol

see also Olive oil Hydroxytyrosol (2-(3,4-dihydroxyphenyl)ethanol, a naturally occurring phenolic compound in olive oil, is a potent antioxidant that prevents lowdensity lipoprotein from oxidation *in vivo* (Grignaffini et al., 1994) as well scavenges free radicals (Visioli et al., 1998). Studies showed



Hydroxytyrosol. (From Vogna et al., *Tetrahedron Lett.*, 44:8289–8292, 2003. With permission.)

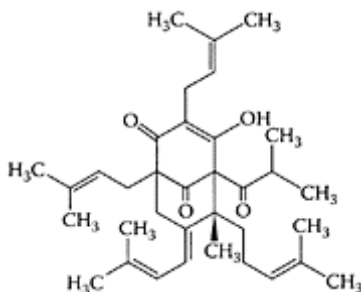
hydroxytyrosol inhibited platelet aggregation and protected against damage by reactive-oxygen species (Petroni et al., 1995; Manna et al., 1997, 1999a, b). The ability of hydroxytyrosol to act *in vivo* was suggested, as it is rapidly taken up by intestinal cell lines by passive diffusion (Manna et al., 2000). Della Ragione and coworkers (2000) found hydroxytyrosol arrested cell proliferation and apoptosis in HL60 cells. They attributed hydroxytyrosol's anti-inflammatory and chemopreventive effects to its ability to downregulate lymphocyte proliferation, which could prove beneficial in the treatment of chronic bowel pathologies, such as Chron's disease.

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Hyperforin

see also St. John's Wort The major lipophilic constituent in the herb St. John's Wort (*Hypericum perforatum*) is the acylphloroglucinol derivative, hyperforin (Laakmann et al., 1998; Singer et al., 1999). In addition to its antibacterial activity (Gurevich et al.,



(From Hostanka, K. et al., *Eur. J. Pharmaceutics Biopharmaceutics*, 56:121–132, 2003. With permission.)

1971), hyperforin was also shown to inhibit the growth of autologous MT-450 breast carcinoma in immunocompetent Wistar rats in a similar manner to that of the cytotoxic drug paclitaxel (Schempp et al., 2002). The antiproliferative and apoptosis-inducing properties of hyperforin were recently demonstrated by Hostanska et al. (2003) in several leukemia cell lines (Figure H.52). Hyperforin treatment of leukemic cells resulted in inhibition of their growth in a dose-dependent manner. Apoptosis was induced by hyperforin in leukemia U937 and K562 cells by enhancement of caspase-9 and caspase-3, and caspase-8 and caspase-3, respectively. They also reported synergism between hyperforin and hypericin, a naphthodianthrone in St. John's Wort, on tumor-growth inhibition.

St. John's Wort (*Hypericum perforatum*) extracts have traditionally been used to treat mild depression, although not all clinical trials have confirmed this property (Whiskey et al., 2001; Kasper, 2001; Bilia et al., 2002). The antidepressant properties of hyperforin were attributed to its ability to inhibit monoamine reuptake (Muller et al., 1997; Chatterjee et al., 1998). These workers showed that in contrast to other antidepressants, hyperforin potently inhibited synaptosomal uptake of the amino acid transmitters GABA and L-glutamate. Roz and coworkers (2002) reported hyperforin inhibited the uptake of monoamines by the rat-brain synaptic vesicles in a dose-dependent manner. To explain this phenomenon, Roz and Rehavi (2003) found hyperforin acted like a protonophore, reducing the pH across the synaptic-vesicle membrane, which interfered with monoamine storage.

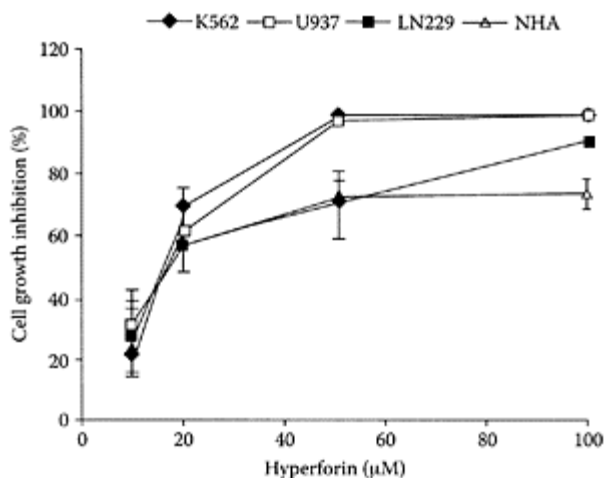


FIGURE H.52 Effect of exposure to hyperforin on cell growth of leukemia K562, U937, LN229, and NHA cells. Cells (5×10^3 /well) were grown for 48 h in the presence of various concentrations of hyperforin and cell growth assessed by the tatrastolium salt, WST-1. (From Hostanska et al., *Eur. J. Pharmaceutics Biopharmaceutics.*, 56:121–132, 2003. With permission.)

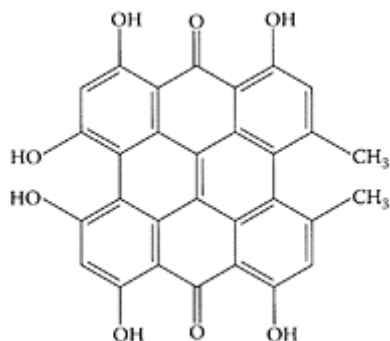
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Hypericin

see also St. John's Wort Hypericin, a naphthodianthrone present in St. John's wort (*Hypericum perforatum* L.), has received increasing attention because of its antiviral, antitumor viral, and photodynamic properties (Gulick et al., 1999; Kamuhabwa et al, 2000; Lavie et al., 1995). In the presence of oxygen and light stimulation, hypericin is one of the most powerful photosensitizers in nature by generating reactive-oxygen species (ROS) capable of destroying tumors (Agostinis et al., 2002). The phototherapeutic properties of hypericin are important in the new therapeutic approach to the treatment of superficial neoplastic lesion, known as photodynamic therapy (PDT). Chen and de Witte (2000) found hypericin was a potent and effective tumor photosensitizer as a PDT tool using a mouse P388 lymphoma-tumor model. Treatment with hypericin (2, 5, and 20 mg/kg, i.p.) 2 h prior to light irradiation significantly ($p < 0.01$) prolonged the life span of the mice (Figure H.53). The efficacy of PDT treatment with hypericin was highest after 2 h compared to 24- and 48-h intervals. Ali and coworkers (2001) showed that photoactivated hypericin induced apoptosis in



Hypericin. (From Hostanska et al., *Eur. J. Pharmaceutics Biopharmaceutics.*, 56:121–132, 2003. With permission.)

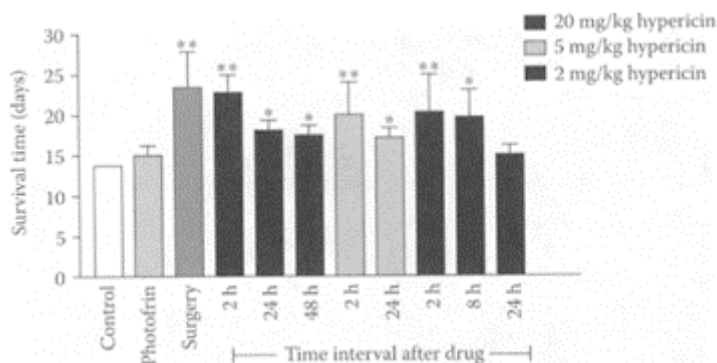


FIGURE H.53 Survival time of DBA/2 mice bearing subcutaneously transplanted P388 lymphoma cells after PDT and surgical excision. Tumor was exposed to 595 nm light 2–48 h after a 2, 5, or 20 mg/kg dose (i.p.) of hypericin and to 630 nm light 24 h after a 5 mg/kg dose (i.p.) of photofrin. For both cases, the light dose was 120 J/cm², delivered at the intensity of 1 mW/cm². The control group shown was the data of tumor-bearing mice without treatment. Each column represents the mean±SD (bars) for at least four animals. ***p*<0.01, **p*<0.05, compared with the control.

(From Chen and de Witte, *Cancer Lett.*, 150:111–117, 2000. With permission.)

human mucosal carcinoma cells by activating caspase proteases, particularly caspase-3.

As an exogenous fluorophore, hypericin showed excellent sensitivity of above 90 percent in the fluorescent diagnosis of bladder cancer, suggesting its use in the early detection of this disease *in situ* (D'Hallewin et al, 2002). Using isolated crayfish neuron, Uzdensky et al. (2003) showed the potential of hypericin and its water-soluble derivative, developed using polyvinylpyrrolidone as carrier, for the visualization and selective photodynamic treatment of malignant gliomas.

The efficacy of St. John's wort for the treatment of mild and moderate depression still remains controversial. Nevertheless, more than 30 clinical trials have found similar efficacy between St. John's wort and low doses of tricyclic antidepressants, without their attendant side effects (Greeson et al., 2001; Schultz, 2002). Simmen and coworkers (2003) examined the effect of three St. John's wort constituents, hyperforin, hypericin, and pseudohypericin. The latter is the hydroxylated derivative of hypericin found in substantially larger amounts compared to hypericin, although no pharmacological effects have yet been ascribed to it. For the first time, these researchers showed the functional antagonism of corticotrophin-releasing factor (CRF₁) receptor by all three compounds, providing evidence for their role in the antidepressant efficacy of St. John's wort. This is because selective CRF₁ receptor agonists represent a new class of anxiolytics/antidepressants. Hypericin and hyperforin affected both CRF and calcitonin, while pseudohypericin selectively antagonized CRF and was considered the only real CRF₁ antagonist.

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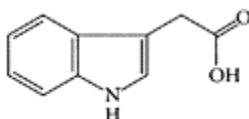
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I

Indole-3-acetic acid (IAA)

Indole-3-acetic acid (IAA) is the major form of the plant hormone, auxin, a key regulator of cell division, elongation, and differentiation in higher plants (Goldsmith, 1993). Recent studies showed that



Indole-3-acetic acid. (Wu et al., *Sens. Actuat.*, B96:658–662, 2003.
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a combination of IAA and horseradish peroxidase (HRP) was cytotoxic to cancer cells and could be used as a novel cancer therapy (Folkes et al., 1998; Greco and Dachs, 2001; Wardman, 2002). IAA must undergo oxidative decarboxylation by HRP before it becomes cytotoxic (Folkes and Wardman, 2001). Since the activated form of IAA produced free radicals, including peroxy radicals, the combination of IAA and horseradish peroxidase could be used to enhance cellular oxidative stress and bring about apoptosis (Candeias et al., 1995). Kim and coworkers (2004) showed that the combination of IAA and horseradish produced free radicals in a dose-dependent manner and induced apoptosis in G361 human melanoma cells. The presence of 1.2 $\mu\text{g/mL}$ of HRP, 100 and 500 μM IAA, caused 50 percent and 100 percent of the cells to die, respectively (Figure I.54). The mechanism involved activation of caspase-8 and caspase-9, which in turn led to activation of caspase-3 and cleavage of poly(ADP-ribose)polymerase. Another examination of the mechanism of IAA cytotoxicity by de Melo et al. (2004) suggested induction of cell death by IAA involved the production of reactive-oxygen species by HRP.

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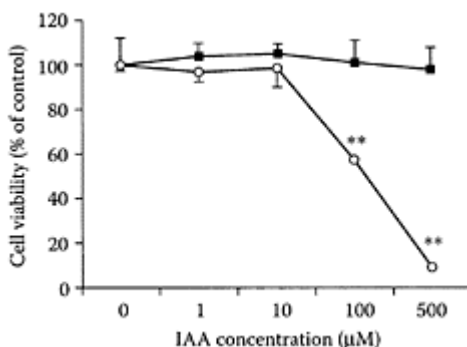


FIGURE I.54 Cytotoxic effect of IAA/HRP in G361 human melanoma cells. After serum-starvation cells were treated with varying concentrations (1–500 μM) of IAA in the absence (■) and presence (○) of HRP (1.2 μg/mL). Each experiment was repeated at least twice, independently and representative results shown. ** $p < 0.01$ compared to the untreated control. (From Kim et al., *Cell Signal*, 16:81–88, 2004. With permission.)

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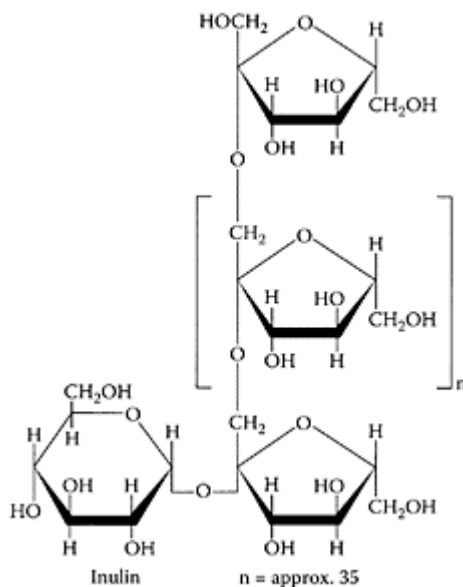
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Indole-3-carbinol

see Diindolymethane

Inulin

Inulin, a naturally occurring, complex polysaccharide present in many plants, is obtained primarily from the roots of chicory (*Cicorium intybus* L.) (De Bruyn et al., 1992) or the tubers of Jerusalem artichoke (Baldini et al., 2003). Chicory inulin is composed of mixtures of linear β 2–1 fructans varying in length from 2 to approximately 65 fructose residues. In comparison, Jerusalem artichoke inulin has a much shorter chain length. The linear 1,2- β -linked D-fructofuranoside chains of inulin are attached via an α 1- β 2 type sucrose linkage to a terminal glucose molecule. The inability of digestive enzymes to digest these 1,2- β -link-ages ensures inulin reaches the gut intact, where it is fermented by the gut flora. In fact, inulin is a prebiotic, stimulating the growth of bifidobacteria and inhibiting colon carcinogenesis in animal models (Reddy et al., 1997; Roberfroid et al., 1998; Reddy, 1999). Causey and coworkers (2000) showed inulin significantly lowered serum triglycerides in hypercholesterolemic men, as well as improved the gut flora. Koo et



al. (2003) found inulin-stimulated NO synthesis *via* activation of protein kinase C (PKC)- α and protein tyrosinase kinase, which activated NF- κ B in RAW 264.7 cells. The release of NO is important for its tumoricidal effects and may explain the anticarcinogenic effects associated with inulin. These results point to inulin having considerable promise as a functional ingredient in the diet.

Videla and coworkers (2001) showed dietary inulin reduced the severity of dextran sodium sulfate colitis in rats. Oral inulin prevented colonic mucosal inflammation by dextran sodium sulfate (DSS) that histologically resembles human ulcerative colitis (Okayasu et al., 1990). In addition to improving histological scores and decreasing the release of inflammatory mediators, it also lowered tissue myeloperoxidase accumulation in DSS colitis in rats. These results suggested inulin may be a useful dietary or pharmacological intervention in patients suffering from ulcerative colitis.

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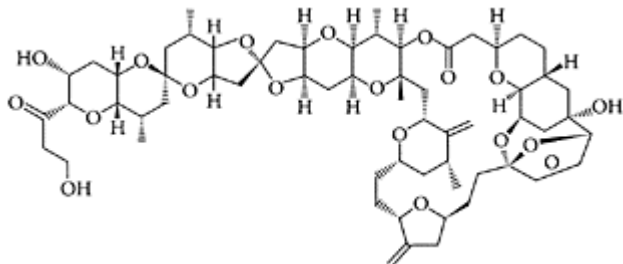
Isoflavones

see also Daidzein and Genistein Isoflavones represent a group of phytoestrogens that are chemically strikingly similar to mammalian estrogens. Phytoestrogens mainly bind to the second subtype of the estrogen receptor (ER β), while mammalian estradiol has a higher binding affinity for the “classic” estrogen receptor ER α (Kuiper et al., 1998; Casanova et al., 1999). They can thus act as either estrogen agonists or antagonists (Setchell, 1998; Setchell and Cassidy, 1999). Legumes are good sources of isoflavones, with soybeans and soy products being the most abundant, containing approximately 0.2–1.6 mg/g dry weight (Kurzer and Xu, 1997). Fitzpatrick (2003) recently reviewed the literature on the effects of soy isoflavones on lipid metabolism, osteoblasts and osteoclasts, bone markers, bone-mineral density, and cognition. Based on very limited human clinical data, it was hard to make definitive recommendations to clinicians other than moderate use for postmenopausal women. The low incidence of breast cancer, cardiovascular disease, and climacteric symptoms in Japanese women compared to Caucasians has been attributed to higher soybean intake. Watanabe et al. (2002) showed a slight improvement in elongation of the menstrual cycle in young women taking an isoflavone-rich tablet. Climacteric women also showed improvement in bone density, hypertension, and climacteric symptoms when maintained on these tablets.

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Isohomohalichondrin B (From Litaudon et al., *Tetrahedron Lett.*, 35:9435–9438, 1994. With permission.)

Isohomohalichondrin B

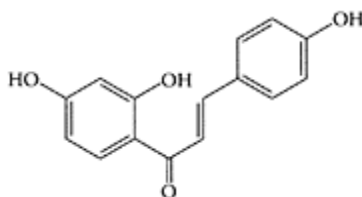
Isohomohalichondrin B (IHB), a member of the halichondrin group, was isolated in New Zealand from the deep-water sponge *Lissodendoryx* sp. It was shown by Litaudon et al. (1994) to be highly toxic towards P388 (murine leukemia) cells. Bergamaschi and coworkers (1999) found IHB to be a potent, antitumor agent delaying cell cycle S-phase progress, mitotic block, tetraploidy, and inducing apoptosis in a human cancer-cell line.

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Isoliquiritigenin

The chalcone isoliquiritigenin (ISL), isolated from licorice and shallots, was shown by Yamamoto et al. (1991) to inhibit the formation of skin papilloma induced by 7,12-dimethylbenz[α]-anthracene (DMBA) and TP (phorbol acetate). Maggolini et al. (2002) reported ISL exhibited both estrogenic and antiproliferative effects on MCF7 breastcancer cells. High concentrations of this phytoestrogen inhibited proliferation of MCF7 cells, while low concentrations stimulated



Isoliquiritigenin. (From Cao et al., *J. Chromatogr.*, A. 1042:203–209, 2004. With permission.)

progression of estrogen-dependent breast tumors. Based on these results, they cautioned that the level of ISL taken by menopausal women be carefully monitored.

The ability of ISL to suppress metastasis of mouse renal-cell carcinoma was reported by Yamazaki and coworkers (2002). The number of metastatic lung nodules was significantly reduced in the presence of ISL. Kanzawa and coworkers (2003) recently reported ISL effectively inhibited prostate cancer. They found that the cell growth of prostate-cancer cell line DU145 was significantly reduced by ISL in a dose- and time-dependent manner (Figure 1.55). The mechanism of action appeared to involve induction of S- and G2/M-phase arrest and was associated with enhanced expression of GADD153. These results suggested ISL was a potential candidate for treating prostate cancer.

The potential of ISL in the treatment of lung cancer was recently demonstrated by Ii et al. (2004). They found ISL inhibited cell proliferation of a human lung-cancer cell line in a dose and time-dependent manner. Cell cycle progression was arrested at the G2/M phase, which was associated with enhanced expression of p21^{CIP1/WAF1}, a universal inhibitor of cyclicdependent kinases.

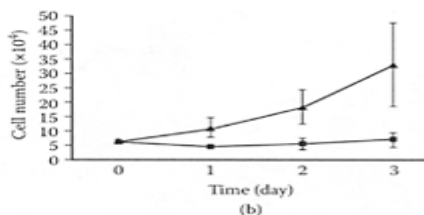
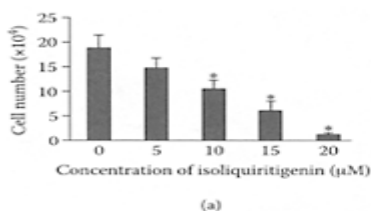


FIGURE I.55 Effect of ISL on the growth of the prostate cancer DU145 cell lines, (a) Dose-dependent effect: cells were exposed for 48 h to various concentrations of ISL or DMSO alone (control), $p < 0.05$ versus control. (b) Time-kinetics study: cells were exposed to 15 μM of ISL for 24, 48, and 72 h. ((▲) DMSO alone (control) (■)) (From Kanzawa et al., *Eur. Urol.*, 43:580–586, 2003. With permission.)

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J

Jasmine (*Jasminum grandiflorum* L.)

While jasmine grows in many parts of the world, jasmine absolute is produced mainly in Egypt by solvent extraction of the essential oil from its delicate flowers. In addition to odorant volatiles, the oil contains fats, pigments, and fatsoluble vitamins. It is used in aromatherapy as a holistic remedy for apathy, fear, hypersensitivity, panic, hysteria, uterine disorders, childbirth pain, skincare, frigidity, coughs, hoarseness, and muscular spasms (Tisserand, 1985; Lawless, 1995).

Konig et al. (1992) developed a GC column using a chiral stationary phase for measuring linalool and jasmine lactone in jasmine oil. Tamogami and coworkers (2001) compared the enantiometric ratios of chiral components in jasmine absolute obtained from Egypt, India, and France. Except for methyl epijasmonate, the other chiral components were not enantiometrically pure. Sensory evaluation indicated that the key flavoring odorants in jasmine were (*R*)- δ -jasmine lactone and (1*R*, 2*S*)-methyl epijasmonate. The very low enantiometric purity of the (1*R*, 2*R*)-enantiomer of methyl jasmonate in Indian juniper probably accounted for the difference in flavor quality compared to those grown in France and Egypt.

Some evidence suggests that spasmolysis or relaxation of smooth muscle in the pig ileum *in vitro* (Lis-Balchin et al., 1996) is correlated with the holistic relaxant effect in man (Lis-Balchin and Hart, 1997). Lis-Balchin and coworkers (2002) reported that jasmine appeared to mediate its spasmolytic action by increasing intracellular cAMP with the possibility of some calcium-channel blockage. They suggested that the pharmacological activity observed in isolated guinea pig ileum may explain the effect of inhaled jasmine vapor by its action on the central nervous system.

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Jerusalem artichoke (*Helianthus tuberosum* L)

see Inulin Jerusalem artichoke, a native North American plant, is capable of enduring high temperatures and severe water-stress conditions. It is one of the richest sources of inulin, a linear polysaccharide of fructose units attached to a terminal sucrose. Baldini and coworkers (2004) evaluated new clones of Jerusalem artichoke, reporting maximum inulin yields up to 8.0 t/ha. Since it cannot be digested by digestive enzymes, inulin enters the intestine intact, where it is fermented by bifidobacteria in the intestine and is therefore considered a prebiotic.

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Jojoba

Jojoba (*Simmondsia chinensis*) is an arid perennial evergreen shrub native to Arizona, California, and northwestern Mexico (Hogan, 1978). The seeds contain a light yellow, odorless wax ester composed of straightchain esters of monounsaturated C₁₈, C₂₀, and C₂₄ acids and alcohols, referred to as jojoba liquid wax. Tobares et al. (2003) found coldpressed wax had the best oxidative stability due to the higher retention of tocopherols and phenolic antioxidants. Jojoba liquid wax has traditionally been used in folk medicine for treating renal colic, sunburn, chaffed skin, hair loss, headache, wounds, and sore throat (Yaron, 1987). Human studies showed that sulfurized jojoba liquid wax was effective in treating acne, while the unmodified wax was used for treating psoriasis

(Mosovich, 1985). The anti-inflammatory properties of jojoba liquid wax were recently demonstrated in several animal models by Habashy et al. (2004). Using the carrageenan-induced rat paw oedema model, jojoba liquid wax significantly reduced edema, as well as decreased prostaglandin E₂ (PGE₂) in the inflammatory exudates in a dose-dependent manner (Figure J.56).

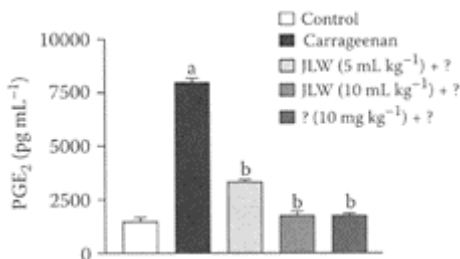


FIGURE J.56 Effect of jojoba liquid wax (JLW) on PGE₂ production in exudates from carrageenan-treated rats.

^aStatistically significant from the control group at $p < 0.05$; ^bStatistically significant from the carrageenan-induced group at $p < 0.05$. (Habashy et al., *Pharmacol. Res.*, 51:95–105, 2005. With permission.)

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Juniper (*Juniperus communis* L.)

Juniper, an evergreen wind-pollinated shrub or small tree, grows extensively in the Northern Hemisphere. Its blue-black berries have a number of pharmacodynamic properties, including diuretic, nephrotoxic, and antioxidative (Sanchez de Medina et al., 1994; Schichter and Leuschner, 1997; Takacsova et al., 1995).

The berries contain an essential oil that is obtained by steam distillation (Newall et al., 1996). The oil is composed mainly of monoterpenes (60 percent), which appear responsible for its biological properties. Filipowicz et al. (2003) recently attributed the antibacterial and antifungal activity of juniper-berry oil to the presence of (-)- α -pinene, *p*-cymene, and β -cymene in the oil. Muhlbauer and coworkers (2003) demonstrated for the first time that essential oils, such as sage, rosemary, pine, turpentine, eucalyptus, and juniper, and their monoterpenes effectively inhibited bone resorption in the rat. The latter has implications in preventing bone loss associated with osteoporosis.

Na and coworkers (2001) showed juniper oil inhibited heat shock-induced apoptosis of human astrocyte CCF-STTG1 cells. Astrocytes are the most abundant glial cell types in the brain, and their death, or apoptosis, has been implicated in the pathogenesis of a number of central-nervous diseases, including Alzheimer's disease. Thus, juniper oil may have therapeutic value in inhibiting astrocyte apoptosis by preventing activation of caspase-3, a key factor in the execution of apoptosis.

Juniper-berry oil is also rich in 5,11,14-eicosatrienoic acid, a polyunsaturated fatty acid similar to that found in fish oil. Jones et al. (1998) found juniper-berry oil was more effective than fish in protecting rat liver from reperfusion injury, a major cause of graft damage in liver transplants, as well as hepatic damage in alcohol-induced liver disease.

The Navajo tribe in northern Arizona and southern Utah have traditionally used ash from the branches and needles of the juniper tree as flavoring in their food products. In addition, a tea is also made from juniper ash to treat diarrhea, as well as injured muscles. Christensen et al. (1998) showed that, in addition to calcium, juniper ash also contributed significant amounts of magnesium and iron in the Navajo diet.

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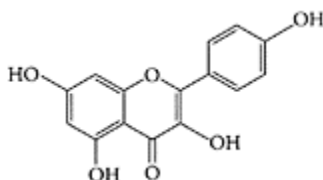
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K

Kaempferol

Kaempferol (3,4',5,7-tetrahydroxyflavone) is a flavonol found in abundance in fruits, vegetables, and tea (Cao et al., 1997; Hertog et al., 1992). It has been shown to have



Kaempferol. (From Tian et al., *J. Mol. Struct.*, 691:197–202, 2004. With permission.)

anti-inflammatory and antioxidant properties in macrophages and neurons. For example, kaempferol protected rat-cortical neurons from amyloid β protein toxicity by minimizing the production of reactive-oxygen species and inhibiting caspase activity (Wang et al., 2001). It was shown previously to reduce prostaglandin E_2 and nitrite production in mouse macrophages by suppressing inducible cyclooxygenase-2 and inducible nitric-oxide synthetase (Liang et al., 1999). Okamoto et al. (2002) examined the immunoregulating properties of kaempferol and found it useful for treating cell-mediated immune diseases, such as acute graft-versus-host disease (GVHD). *In vitro* studies with mice-spleen cells showed kaempferol acted directly on T cells by inhibiting Th1 cytokine production and suppressing expansion or generation of CD8⁺ CTLs. Subsequent treatment of C57BL/6-into-BDF 1 mice with kaempferol reduced GVHD-associated antihost CTL activity by activating Th2 cells and engraftment of the donor cells. The overall result was early recovery of body weight loss, increased survival, and reduced injury to the liver and large intestine.

Recent data suggest tea and vegetable consumption, such as onions, can provide protection against osteoporosis in older women (Hegarty et al., 2000; Muhlbauer and Li, 1999; New et al., 2000; Muhlbauer et al., 2002). This was attributed to the presence of flavonols, such as quercetin and kaempferol as rutin, a glycoside of quercetin. Rutin was shown previously by Horcajada-Molteni and coworkers (2000) to inhibit ovariectomy-induced osteopenia in rats. Using osteoclasts from 10-day-old rabbits, Wattel et al. (2003) showed kaempferol and quercetin both reduced bone resorption in a time- and dose-

dependent manner (Figure K.57). Both flavonols induced apoptosis of mature osteoclasts in the same dose range that effectively inhibited bone resorption. Treatment of highly purified rabbit osteoclasts with 50 μM quercetin and kaempferol significantly reduced intracellular levels of reactive-oxygen species by 75 percent and 25 percent, respectively. Below this concentration, neither of these flavonols exhibited any antiradical activity, so that their antioxidant activity could not explain their inhibitory effect on bone resorption. However, they found that only kaempferol's inhibition of bone resorption was partially reduced by addition of a pure antiestrogen. This suggested that inhibition of bone resorption by kaempferol could be partly explained by its estrogenic effect. This study demonstrated the importance of dietary sources of flavonols, such as kaempferol, as inhibitors of osteoporosis.

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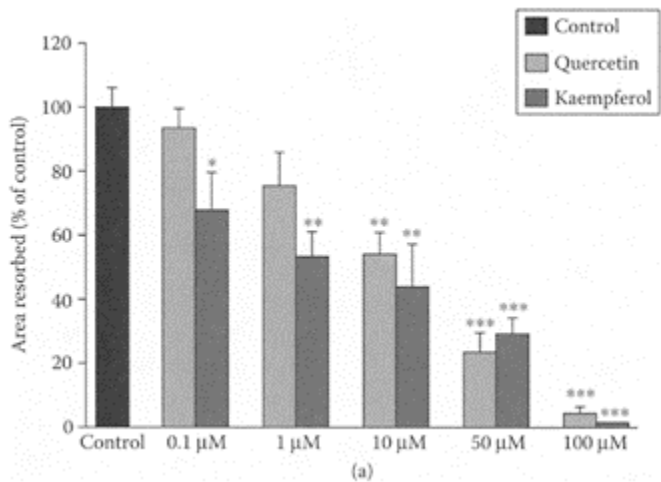


FIGURE K.57 Effect of different concentrations of quercetin and kaempferol on osteoclastic bone resorption. Osteoclasts were cultured on cortical bovine slices during 48 h in media containing either vehicle (0.1 percent DMSO—control) or flavonols,

quercetin, and kaempferol (0.1–100 μ M), and bone resorption assessed by measurement of total area of resorption pits. Results expressed as percent of control. Values are mean \pm SEM of three independent experiments (N=5 for pit-area measurement); (*) $p < 0.05$, (**) $p < 0.01$, and (***) $p < 0.001$ compared with control group. (Wattel et al., *Biochem. Pharmacol.*, 65:35–42, 2003. With permission.)

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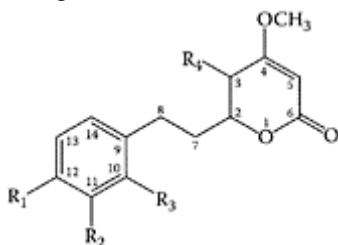
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Kava-kava

Kava-kava (*Piper methysticum*), a plant native to the Pacific Islands, has been used for its soporific and narcotic effects (Bilia et al., 2002). Extracts were traditionally prepared from its macerated roots by mixing with water and coconut milk (Norton and Ruze,



Kavalactones	R ₁	R ₂	C5-C6	C7-C8
Kacain				=
7,8-Dihydrokavain				
Methysticin	OCH ₂ O			=
Dihydromethysticin	OCH ₂ O			
Yanгонin	OCH ₃		=	=
Desmethoxyyangonin			=	=
5,6,7,8-Tetrahydroyangonin				

SCHEME K.31 Kavalactone structures. (Adapted from Bilia et al., *J. Chromatogr. B.*, 812:203–214, 2004.)

1994). The active ingredients in kava-kava, known for their analgesic and anesthetic properties, are a group of lipophilic lactone derivatives with an arylethylene- α -pyrone skeleton. The major lactones are (+) kavain, (+)-methysticin, desmethoxyyangonin, yangonin, (+)-dihydrokavain, (+)-dihydromethysticin, and tetrahydroyangonin. Minor components include chalcones and essential oil. The kavalactone structures are shown in Scheme K.31.

In vitro studies showed isolated kavalactones directly affected the central nervous system and neurotransmitters by interacting with GABA-benzodiazepine receptors and by inhibiting noradrenaline uptake (Davies et al., 1992; Jussofie et al., 1994). Inhibition of noradrenaline uptake by kavalactones may explain some of their psychotropic properties (Seitz et al., 1997). The ability of kava-enriched extracts to inhibit human platelet MAO-B may also be an important mechanism for their psychotropic properties (Uebelhack et al., 1998).

Extensive clinical studies, using a number of rating scales (Hamilton Anxiety Scale and Clinical Global Impressions Scale), all showed the efficacy of kavalactones as an

anxiolytic drug. For example, Lehmann et al. (1996) demonstrated the effectiveness of kava-kava extract for treating anxiety disorders, while Voltz and Kieser (1997) showed the same extract significantly improved patients suffering from anxiety of nonpsychotic origin. Overall, studies showed good tolerance and low incidence of adverse effects associated with kava-kava treatment, including a systematic review and meta-analysis (Pittler and Ernst, 2000). Cagnacci and coworkers (2003) recently found an improvement in the mood of perimenopausal women, particular in anxiety, following administration of kava-kava. Lehl (2004) reported that sleep disturbances associated with nonpsychotic disorders were effectively and safely treated with a kava extract WS®1490.

A number of adverse cases, however, were reported in Germany, where kava-kava was associated with dopamine antagonism (Schelosky et al., 1995), while seven cases of hepatitis were attributed directly to kava-kava intake (Strahl et al., 1998; Escher et al., 2001; Russmann et al., 2001). Stickel and coworkers (2003) pointed to the potential hepatotoxicity of kava in Germany, which led to hepatic necrosis or cholestatic hepatitis in patients given alcoholic and acetonic kava extracts. High doses of kava lactones were recently shown by Gow et al. (2003) to have serious hepatotoxic side effects. Such lactones are normally metabolized by the cytochrome P450 system in the liver (Schmidt et al., 1999) and by lactone hydrolases in the serum (Bargota et al., 2003). A recent study by

TABLE K.40
Extraction of Kava Lactones from Roots of *P. Methysticum* with Different Solvents¹

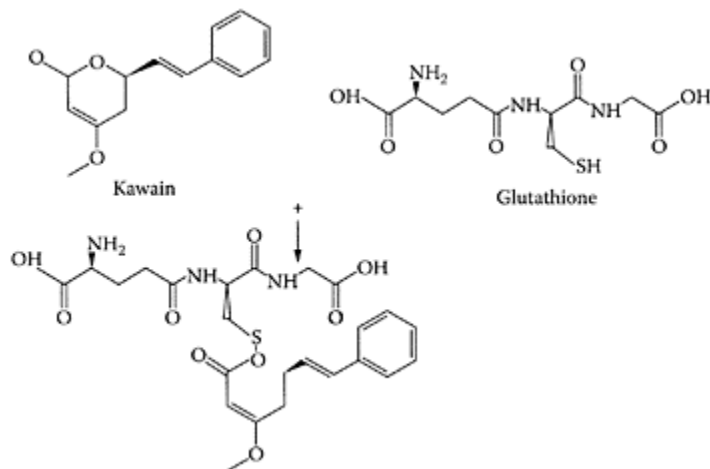
Extract	Percent Kava Lactones in Dried Extract
Acetone extract (standardized method)	100(0.001)
96 percent ethanol extract (standardized method)	100(0.001)
25 percent ethanol (traditional method)	15(0.02)
Water (traditional method)	2.97(0.03)

¹ Data presented as means (and standard deviation) for 10 samples in each solvent.

Source: Adapted from Whitton et al., *Phytochemistry*, 64:673–679, 2003. With permission.

Whitton et al. (2003) attributed the toxicity of kava-kava lactones to the particular extraction method, as they were 30 times higher in the standardized preparations compared to the traditional aqueous-extraction method. The various solvents used to extract kava lactones resulted in markedly different yields in the dried extract, ranging from 100 percent for the standardized methods involving acetone or 96 percent alcohol to 15 percent and 2.97 percent using the more traditional extractants of 25 percent ethanol or water, respectively (Table K.40). The higher levels in the more standardized extracts would saturate the detoxification pathways leading to hepato side effects. Since glutathione plays a crucial role in the phase II conversion of lactones to excretable waste products, its depletion could explain the increased side effects observed for kavalactones. Schmidt and coworkers (2001) reported that sesquiterpene lactones bind to glutathione, allowing faster clearance by lactone hydrolases in the hepatocytes. Whitton and

coworkers (2003) showed that supplementation with glutathione rendered the kava lactone nontoxic to eukaryotic cells by a similar mechanism in which the lactone ring was opened up via the Michael reaction (Scheme K.32), bypassing the cytochrome P50 pathway. The adverse hepatotoxic effects were found with the tablets and capsules made using standardized kava extracts in which glutathione was either absent or present at very low levels. Traditional preparations, on the other hand, contained high levels of glutathione, which probably



SCHEME K.32 The Michael reaction between kawain and glutathione.

(From Whitton et al., *Phytochemistry*, 64:673–679, 2003. With permission.)

explains their safe use for many years. To avoid these adverse effects, supplementation with glutathione appears to be essential. The recent banning of kava in the U.K. and Europe is presently under review.

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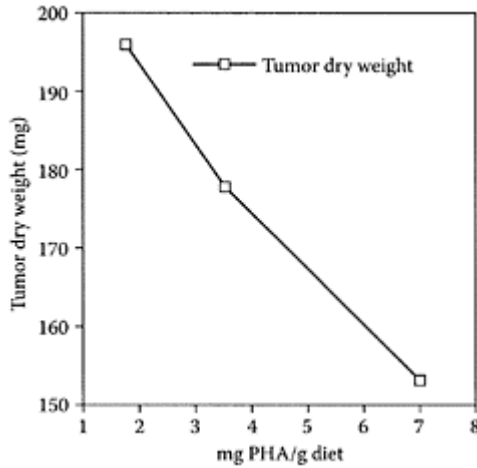


FIGURE K.58 Tumor growth expressed as dry tumor mass related to body dry weight in mice fed diets containing increasing amounts of phytohemagglutinins (PHA). (Pryme et al., *Cancer Lett.*, 146:87–91, 1999. With permission.)

Kidney Bean

see also Beans and Lectins Kidney beans (*Phaseolus vulgaris*) are a variety of beans with a dark, red skin. Like most legumes, kidney beans contain a toxic lectin component that is normally inactivated by boiling to prevent gastric upset. Lectins or phytohemagglutinins, however, have been shown to exert beneficial health benefits. A number of studies reported that phytohemagglutinin in raw kidney bean diminished the growth of Krebs II non-Hodgkin lymphoma tumors in NMRI mice (Pryme et al., 1994a, b, 1996). Pryme and coworkers (1999) found that phytohemagglutinins curtailed the growth of established nonHodgkin lymphoma tumors (five days after tumor development was initiated) by as much as 30–40 percent in female NMRI mice fed diets containing increasing levels of phytohemagglutinins in a dose-dependent manner, as shown in Figure K.58. These results further confirm the importance of red kidney bean as a functional food due, in part, to the presence of bioactive lectins.

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Kiwifruit

Kiwifruit has become extremely popular over the past decade. Two varieties are grown, one with green flesh and the other with yellow flesh. In addition to being a rich source of vitamin C, those grown in Asia have been used in Chinese traditional medicine for the treatment of different cancers (Zhi, 1980). Sheng (1984) reported a 30–40 percent inhibition of sarcoma in mice fed kiwifruit, while Song (1984a, b) showed kiwifruit juice inhibited cancer-cell growth. Using the Ames' test, Liu and Peng (1994) found that some kiwi-fruit extracts exhibited a 95 percent inhibition of cancer. Motohashi and coworkers (2002) recently reported valuable bioactive compounds in kiwi gold fruit extracts. For example, hexane and acetone extracts proved selectively cytotoxic against human oral cell lines, while the more hydrophyllic 70 percent methanol fractions had higher anti-HIV, radical-generating, and O₂⁻-scavenging activities.

An antifungal, thaumatin-like protein composed of a single-chain 21 kDa was isolated by Wang and Ng (2002) from the green-flesh kiwifruit variety. The N-terminal sequences of thaumatin-like proteins (TLP) from mono- and dicotyledons exhibited 65–80 percent identity with TLP from kiwifruit (Table K.41). Of particular note was the presence of the fifth residue (F) not present in any of the other TLPs. The

TABLE K.41
Comparison of N-Terminal Sequences of
Kiwifruit TLP with Other TLPs¹

Amino Acid	Residue Number	Identity	Percent
Kiwi TLP	1	<u>ATFNFI-NNCPFTVWAAAVP-G</u>	100
French Bean TLP	1	<u>ANFN-IVNNCPYTVWAAASP-G</u>	80

Wheat TLP	26	<u>ATFN·IKNNCPYTVWPAATPIG</u>	80
Barley TLP	1	<u>ATFTVI·NKCQYTVWAAAVPAG</u>	75
Maize TLP	1	<u>AVFTVV·NQCFTVWAAASVP·G</u>	65
Rice TLP	32	<u>ATF·AITNRCQYTVWPAAVPSG</u>	70
Chickpea TLP	22	<u>ANFE·IVNNCPYTVWAAASP·G</u>	75
Flaxseed TLP	1	<u>ARFD·IQNKCPYTVWAAASVP·G</u>	70
Grape TLP	25	<u>ATFD·ILNKCTYTVWAAASP·G</u>	70

¹ Above sequences were obtained from a BLAST search and are aligned for maximal similarity. Amino-acid residues identical to the corresponding residues in kiwifruit TLP are underlined. Aminoacid residue number 26 for wheat TLP refers to A being the 26th amino-acid residue in the TLP.

Source: From Wang and Ng, *Phytochemistry*, 61:1–6, 2002. With permission.

kiwi protein exerted antifungal activity against *Botrytis cinerea* and suppressed *Mycosphaerella arachidicola* and *Coprinus comatus*. Wang and Ng (2002) also found that kiwi TLP inhibited HIV-1 reverse transcriptase, similar to that reported for French bean TLP (Ye et al., 1999).

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Kurosu

Kurosu is one of the traditional vinegars in Japan produced from unpolished rice by fermentation. It has been reported to have medicinal properties, such as improving blood fluidity and preventing hypertension (Nishikawa et al., 2001). Studies by Nishidai and coworkers (2000) showed an ethyl-acetate extract from Kurosu exhibited both antioxidant activity, as well as antitumor properties in mice. Shimoji et al. (2002) first identified dihydroferulic acid and dihydrosinapic acid as the major phenolics in Kurosu responsible for its radicalscavenging activity. These compounds were present at much higher levels in Kurosu compared to common rice vinegar (polished-rice vinegar), as shown in Table K.42. The higher content of antioxidant compounds in Kurosu, particularly dihydroferulic and dihydrosinapic acids, probably explains the almost twofold greater scavenging activity by Kurosu compared to rice vinegar.

TABLE K.42

Content of Antioxidative Compounds and Dihydroferulic Acid and Dihydrosinapic Acid in Kurosu and Rice Vinegar and Their I_{50} in DPPH Radical-Scavenging Activity

	Content (mg/L) in Kurosu	Content (mg/L) in Rice Vinegar	IC_{50} (μ g/mL)
Kurosu Concentrate	29400		1710
Rice Vinegar Concentrate		23800	3340
Dihydroferulic Acid	24.8	0.09	15.1
Dihydrosinapic Acid	4.68	n.d. ^a	10.1

^a Not detected.

Source: From Shimoji et al., *J. Agric. Food Chem.*, 50:6501–6503, 2002.

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L

α -Lactalbumin

α -Lactalbumin, the major protein regulator of lactose synthase in milk, has the highest content of tryptophan (Trp) and the highest Trp/ Σ Large neutral amino-acids (LNAAs) ratio among food-protein sources (Heine et al., 1996). Tryptophan is the precursor of brain serotonin (5-hydroxy-tryptamine, 5-HT), which is involved in mood disorders, such as anxiety and depression (Berk, 2000). Consequently, tryptophan was proposed as a possible treatment for depression (Meyers, 2000; Young, 2000). Because of its high level of tryptophan, Markus et al. (2000) showed that ingestion of α -lactalbumin reduced depressive feelings in stress-vulnerable human subjects compared to a casein-enriched diet. Using male Wistar rats, Orosco and coworkers (2004a) also found that ingestion of an α -lactalbumin-enriched diet induced anxiolytic and rewarding effects compared to an enriched casein diet. These effects may be related to the enhanced release of serotonin in the medial hypothalamus in rats fed 30 min meals (acutely) but disappeared after 3–6 days of diet (chronic). Based on their research findings, together with the study by Markus et al. (2003), diets enriched with α -lactalbumin appeared to be beneficial in treating stress and anxiety in the short term.

Pelligrini et al. (1999) identified antimicrobial peptides in bovine α -lactalbumin by isolating and characterizing three bacteriocidal domains. Oevermann and coworkers (2003) showed that chemical modification of the lysine residues with 3-hydroxyphthalic anhydride (3-HP) in several bovine milk protein fractions, including α -lactalbumin, yielded compounds with antiviral activity against human herpes simplex virus type 1 (HSV-1). Digestion of these modified proteins produced short peptides that had considerable potential for the treatment of herpes, as they were economical, as well as exhibited reduced antigenicity. Supplementation of an infant formula with α -lactalbumin and glycomacropeptide by Bruk et al. (2002) also benefited the human microflora by significantly reducing the presence of pathogenic bacteria.

Opioid active peptides are released from milk proteins, such as α -lactalbumin, by enzymatic hydrolysis. For example, α -lactorphin, a tetrapeptide (Tyr-Gly-Leu-Phe) released by peptic or tryptic hydrolysis of α -lactalbumin, had an amino-acid sequence corresponding to residues 50–53 in the original intact protein (Antila et al., 1991). The opioid properties associated with α -lactorphin reflected the similarity between its amino acid sequence and the N-terminal amino-acid residues of opioid peptides, such as β -endorphin, enkephalins, and dynorphin (Tyr-Gly-Gly-Phe) (Teschemacher et al., 1997). α -Lactorphin was found by Nurminen et al. (2000) to lower blood pressure in

spontaneously hypertensive rats with established hypertension. Sipola and coworkers (2002) showed α -lactorphin improved vascular relaxation in the spontaneously hypertensive rats and involved nitric oxide but not vasodilatory prostanoids.

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SCHEME L.33 Proposed roles for lactoferrin. (From Brock, *Biochem. Cell. Biol.*, 80:1–6, 2002. With permission.)

Lactoferrin and Lactoferricin

see also Bovine lactoferrin Lactoferrin, an ironbinding glycoprotein present in milk, is a multifunctional protein with immunomodulation and antimicrobial activity (Vorland, 1999; Weinberg, 2001; Farnaud and Evans, 2003). These many roles for lactoferrin are summarized in Scheme L.33. In contrast, lactoferricin is a peptide released from the N-terminal part of lactoferrin by peptic digestion (Tomita et al., 1991). Compared to lactoferrin, a bilobal glycoprotein with a mass of 80 kDa, the lactoferricin-peptide structure is a loop with a cationic charge, containing 25 amino acids in the case of bovine lactoferricin (Lfcin B) and 47 aminoacid residues for human lactoferricin (Lfcin H) (Scheme L.34).

Lactoferrin is a potent inhibitor of different enveloped viruses, including herpes simplex virus (HSV) 1 and 2 (Marchetti et al., 1998), human immunodeficiency virus (HIV) (Puddu et al., 1998), human cytomegalovirus (Portelli et al., 1998), and human hepatitis C virus (Ikeda et al., 1998), as well as two naked viruses, SA11 rotavirus and poliovirus type 1 (Marchetti et al., 1999; Superti et al., 1997). Arnold and coworkers (2002) found lactoferrin was the only milk protein that inhibited adenovirus replication in a dose-dependent manner by preventing replication at an early phase of viral replication.

Bovine and human lactoferricin (Lfcin B and Lfcin H) were both shown to exhibit antiviral activity against human cytomegalovirus

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Lactokinin

Lactokinin is a short, biologically active peptide released by tryptic digestion of the whey milk protein β -lactoglobulin (Ala-Leu-Pro-His-Ile-Arg) (Mullally et al., 1997). It inhibits angiotensin-1-converting enzyme (ACE), an enzyme associated with the renninangiotensin system that regulates peripheral blood pressure, reducing blood pressure in hypertensive individuals. Fitzgerald and Meisel (1999) suggested that while ACE inhibitors derived from whey protein were not as potent as synthetic antihypertensive drugs, they were sufficiently active to exert an antihypertensive effect. Vermeirssen and coworkers (2002) reported that lactokinin was partly transported through a caco-2 cell monomer. Maes and coworkers (2004) showed for the first time that lactokinin modulated the release of endothelin1 (ET-1) by porcine aortic endothelial cells (Figure L.59). ET-1 is a vasoconstrictive peptide that acts via a specific receptor. Compared to 0.1 mM of the drug captopril, which decreased ET-1 release by 42 percent, lactokinin produced a 29 percent decrease under the same conditions. Thrombrin significantly stimulated the basal release of ET-1 by 66 percent.

While incubation with 1 μ M and 0.1 nM of captopril inhibited the stimulated ET-1 release by 45 percent and 62 percent compared to 32 percent and 43 percent when thrombrin was coincubated with 1 μ M and 0.1 mM of lactokinin. While lactokinin was not quite as effective as captopril, nevertheless, this milk-proteinderived peptide could still be a useful treatment of hypertension. Recent data by Maes et al. (2004) showed lactokinin modulated ET-1 release by endothelial cells, which explained the antihypertensive effect of milk-protein peptides.

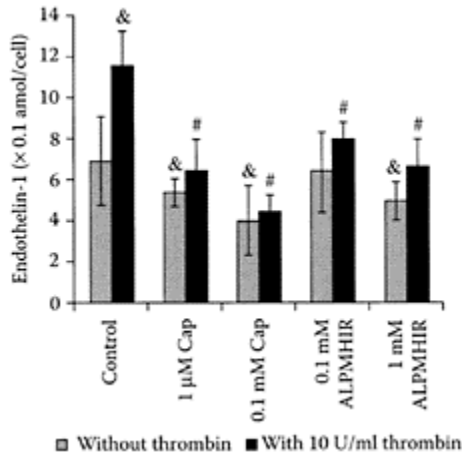
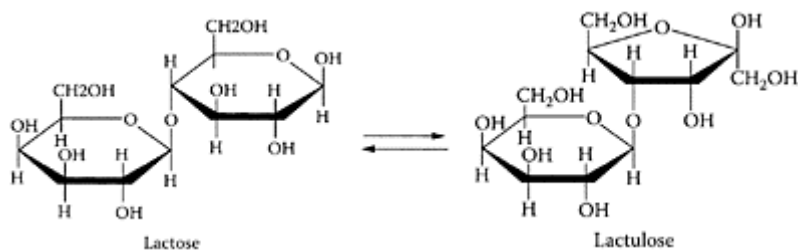


FIGURE L.59 Effect of captopril and lactokinin on basal and 10 μ /mL thrombrin-stimulated endothelial release by porcine aortic endothelial cells. Drugs and peptide were solubilized in medium 199 supplemented with 190 porcine serum. Cells were exposed to medium 199 with 1 percent serum, 1 μ M and 0.1 mM captopril (cap), 0.1 and 1.0 mM lactokinin (ALPMHIR), with or without the addition of 10 μ /mL thrombrin (throm). [&] Different from ET-1 release without stimulation, $p < 0.01$. [#] Different from 10 μ /mL thrombrin-stimulated ET-1 release, $p < 0.01$. Values are means \pm 2 SD., $n = 10 - 15$. (Maes et al., *Reg. Pept.*, 118(1-2): 105-109, 2004. With permission).

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SCHEME L.35 Alkaline isomerization of lactose to lactulose. (From Montilla et al., *Food Chem.*, 90:883–890, 2005. With permission.)

Lactulose

Lactulose (4-O- β -D-galactopyranosyl-D-fructose), an isomerized product of lactose (Scheme L.35), is a registered medicinal drug in more than 100 countries (Schumann, 2002). While it does not occur naturally in milk, it is present in very small amounts in heated milk and in UHT milk. Unlike the α 1–4 glycosidic bond in lactose, the β 1–4 glycosidic bond in lactulose cannot be broken down by the digestive enzymes, so it passes through to the intestine, where it is metabolized by the colonic bacteria. Lactulose is a prebiotic, as it is the preferred food for lactic-acid bacteria compared to the proteolytic activity of various pathogenic bacteria in the colon. It is effective in the treatment of chronic constipation and is the standard, worldwide treatment for hepatic encephalopathy (Blei and Cordoba, 2001).

Lactulose also prevents tumors by protecting DNA in human-flora associated rats exposed to dimethylhydrazine (DMH) (Rowland et al., 1996). Although very little

lactulose is absorbed (0.25–2 percent), it appears to have specific beneficial immunological effects when given intravenously or *in vitro* (Greve et al., 1980; Liehr and Heine, 1981). Lactulose has been found to reduce urinary tract infection (UTI) and pneumonia (McCutcheon and Fulton, 1989) and stimulate calcium absorption in post-menopausal women (Van de Heuvel and Weidauer, 1999). A preparation containing lactulose was reported by Bianchi and coworkers (1994) to lower blood glucose. Lhoste et al. (2001) reported Fischer male rats inoculated with *Clostridium paraputrificum* fed lactulose-enriched diets increased butyrate in the caecum. The formation of butyrate has a number of beneficial effects, including preventing carcinogenesis (see butyric acid).

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Lavender (*Lavandula angustifolia*)

Lavender oil, used in aromatherapy, is obtained from the flowering tips of the plant *Lavandula angustifolia*. Shellie and coworkers (2002) identified 85 components in lavender essential oil, which accounted for more than 95 percent of the oil. Of nine samples analyzed, three were closest to the ISO Standard 3515, which included acceptable ranges for linalool, 25–38 percent; linalyl acetate, 25–45 percent; lavandulyl acetate minimum, 2 percent; terpinen-4-ol, 2–6 percent; lavandulol minimum, 0.3

percent; 1,8-cineole, 0–15 percent; limonene, 0–0.5 percent; trans β -ocimene, 2–6 percent; cis- β -ocimene, 4–10 percent; 3-octanone, 0–2 percent; camphor, 0–0.5 percent; and α -terpineol, 0–1 percent. Lavender oil is a holistic relaxant thought to have carminative, antifatulence, and anticolic properties (Tisserand, 1985). The oil was found to have a spasmolytic effect on guinea-pig ileum *in vitro* (Lis-Balchin et al., 1996), which is correlated with the holistic relaxant effect in man (Lis-Balchin and Hart, 1997). The spasmolytic effect of lavender and linalool were shown by Lis-Balchin and Hart (1999) to be mediated via cAMP.

The impact of aromatherapy on positive mood shifts by Knasko (1992) led to a study on the effect of lavender baths on psychological well-being by Morris (2002). Forty female university students and staff, with a mean age of 28.2 years, were randomly allocated either grapeseed oil or 80 percent grapeseed oil and 20 percent lavender oil to use in their daily bath for 14 days. Using the University of Wales Institute of Science and Technology (UWIST) Mood Adjective Checklist (Matthews et al., 1990), lavender oil was found to have a selective effect on anger-frustration in the first trial, while reducing negative responses about the future in the second trial. These results suggested lavender-oil baths may have a positive effect on psychological well-being. A recent study by Fernandez and coworkers (2004) showed differences in response to odors between newborn infants of depressed and non-depressed mothers. Only newborn infants of depressed mothers increased relative left frontal electroencephalographic (EEG) asymmetry following exposure to lavender or rosemary aroma, with no response by newborns of non-depressed mothers. The shift in right frontal EEG asymmetry is a pattern associated with a positive effect and response to positive stimuli and was related to significantly greater head turning and lip licking. A recent review of the scientific and clinical evidence for the psychological effects of lavender was prepared by Kirk-Smith (2003).

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Lectins

Lectins are glycoproteins that combine reversibly with sugars and glycoconjugates. They cause agglutination of erythrocytes, as well as interfere with nutrient absorption by binding with glycoproteins on the epithelial surface of the small intestine (Lajolo and Genovese, 2002). They are found as phytohemagglutinins in a wide variety of plants, particularly legumes. Lectins may have possible medical uses by their ability to provoke hyperplasia of the small intestine, alter the bacterial flora, and interfere with hormone secretion, as well as enter systematic circulation (Pusztai, 1993; Pusztai and Bardocz, 1996). For example, mice fed a purified bean phytohemagglutinins had reduced tumor growth, indicating competition between the gut epithelium undergoing hyperplasia and the growing tumor (Pusztai et al., 1998). Gastman et al. (2004) reported wheatgerm agglutinin induced apoptosis by binding to surface carbohydrates (*N*-acetylmeuraminic or *N*-acetylglucosamine) of normal and malignant cells. The lectin-induced apoptosis was extremely fast and mediated via a mitochondrial pathway.

The possible use of lectins for treating obesity was shown by Pusztai and coworkers (1998) by the reduction in lipid accumulation in obese rats fed a diet containing raw kidney beans. This was attributed to a reduction in insulin levels by the bean lectins with no loss in body or muscle proteins observed.

Nishimura and coworkers (2004) recently found that bone-marrow mesenchymal stem cells, chondrocytes, and osteoblasts exposed to a lectin from the bean (*Phaseolus vulgaris*) increased their adhesion on plastic culture dishes or plates of hydroxy apatite, titanium, and poly-DL-lactic-co-glycolic acid (PLGA). The bean lectin, erythroagglutinin, enhanced resistance of these cells to proteases and mechanical stimuli, suggesting their potential in tissue engineering and cell therapy.

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Legumes

see also Beans, Bowman-Birk protease inhibitors, Chickpea, Kidney bean, Lectins, Lentils, Peas, Resistant starch, and Soybeans Legumes play an important role in human nutrition, as they are excellent sources of proteins and complex carbohydrates. In addition to being good sources of vitamins and minerals, legumes are considered low glycemic foods, as they elicit a low blood-glucose response (Tharanathan and Mahadevamma, 2003). Legumes have long been recognized as beneficial for controlling and treating metabolic diseases, such as diabetes mellitus, coronary heart disease, and colon cancer (Simpson et al., 1981). They are consumed as whole or grains, dehusked, or as split legumes and include peas, lentils, and a variety of beans, such as red gram, black gram, cowpea, broad bean, field bean, horse bean, and kidney bean.

A number of dietary components in legumes appear to be responsible for their beneficial physiological effects, including protein and starch. Chau and coworkers (1998) incorporated 12 percent protein concentrates from three Chinese legume seeds, *Phaeolus angularis*, *Phaseolus calcaratus*, and *Dolichos lablab* in the diets of male Golden Syrian hamsters and found a pronounced hypocholesterolemic effect. The three legume-protein concentrates significantly ($p < 0.05$) lowered serum triglyceride and total and LDL cholesterol levels and liver total lipids and cholesterol compared to casein. The more potent hypocholesterolemic effects were associated with *P. calcaratus* and *D. lablab*, while only the former significantly increased serum HDL cholesterol. During processing, the higher amylose content (30–40 percent) of legume starches compared to cereals (Madhusudhan and Tharanathan, 1995) results in the formation of large amounts of resistant starch. The latter is known to have important physiological benefits (Edwards, 1993).

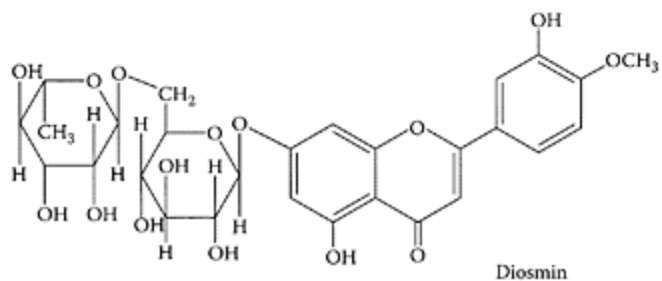
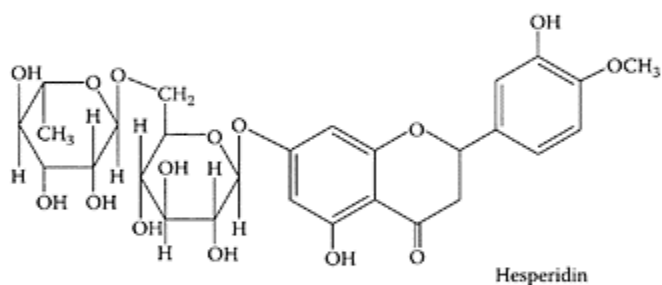
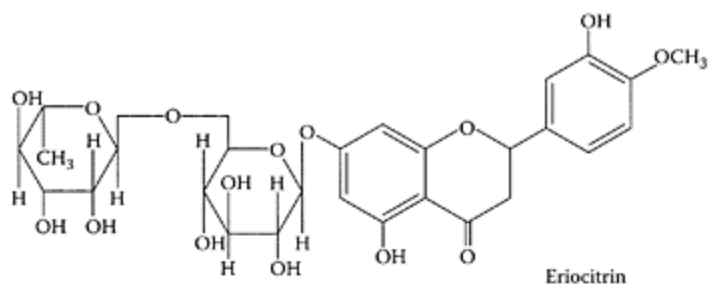
Legumes are also rich in protease inhibitors and lectins, considered antinutritional factors (Lajolo and Genovese, 2002). However, the

Bowman-Birk inhibitor was shown to have therapeutic properties that included anticarcinogenic and antiinflammatory, as well the ability to reduce ulcerative colitis in mice (Kennedy, 1998; Wan et al., 1999; Ware et al., 1999; Armstrong et al., 2000).

Lectins are also recognized for their beneficial properties, including preventing gastrointestinal atrophy during total parenteral nutrition and reducing tumor growth in mice, as well as treating obesity (Pryme et al., 1998; Pusztai et al., 1998; Jordinson et al., 1999).

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Eriocitrin, hesperidin, and diosmin. (From Del Rio et al., *Food Chem.*, 84:457–461, 2004. With permission.)

Lemon

see also Flavonoids and Hesperidin Lemon juice is a rich source of ascorbic acid and flavonoids. The antioxidant properties of these compounds have been suggested to inhibit heart disease and certain types of cancers (Salah et al., 1995). Marin and coworkers (2002) found these nutraceuticals were higher in Fino lemon juice compared to the Vern variety. In addition, they found that different industrial-extraction systems affected the

levels of these components. Miyake et al. (1997) identified the flavonoid, eriocitrin, in lemon fruit, which had considerable antioxidant activity. Ogata and coworkers (2000) showed this flavonoid induced apoptosis in HL-60 cells and may have therapeutic applications. A recent study of *Citrus limon* flavonoids by Del Rio et al. (2004) found that immature fruit from Lisbon and Fino-9 cultivars were excellent sources of the flavonone hesperidin, while mature fruits from Fino-9 and leaves of Eureka were good sources of the flavone diosmin and the flavonone eriocitrin. Each of these flavonoids have been shown to have pharmaceutical properties.

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Lemon balm (*Melissa officinalis*)

The leaves of lemon balm, a perennial, lemon-scented herb, are used extensively as an herbal tea in Europe for its aromatic, digestive, and antispasmodic properties in treating sleep disturbances and gastrointestinal disorders (Bisset and Wichtl, 1994). It is generally sold in combination with other herbs that elicit “calming” or sedative effects. Cerny and Schmid (1999) showed that a combination of valerian and lemon balm significantly improved the quality of sleep of healthy volunteers during 30 days of treatment with 360 mg/day and 240 mg/day of valerian and lemon balm, respectively. Acute administration of lemon balm was shown by Kennedy and coworkers (2002) to modulate the mood and cognitive performance of healthy volunteers in a dose- and time-dependent manner, as assessed using the Cognitive Drug Research (CDR) computerized-test battery and two serial subtraction tasks. The calming effect and possible cholinergic modulation of lemon balm may have application in the treatment of Alzheimer’s disease. A recent double-blind, placebo-controlled study using lemon balm essential aromatherapy on 71 patients suffering from severe dementia by Ballard et al. (2004) also showed they were less agitated and socially withdrawn compared to the placebo.

Carnat and coworkers (1998) reported the presence of 0.13 percent citral (neral+geranial) and 11.8 percent total polyphenolic compounds in the essential oil of dried lemon-balm leaves. Of the latter, hydroxycinnamic compounds accounted for 11.3 percent, with rosmarinic acid 4.1 percent, and total flavonoids 0.5 percent. Herbal tea from lemon balm contained 10 mg/L essential oil, of which 74 percent was citral plus large amounts of polyphenolic compounds.

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Lemon Grass (*Cymbopogon citratus*)

Lemon grass, native to India, is used in Thai and Vietnamese cooking. Most commercial crops for the United States are grown in California and Florida. Using the Salmonella mutation assay, Vinitketkumnuen and coworkers (1994) showed an ethanol extract from lemon grass exhibited antimutagenic activity against a number of different mutagens. Anticancer components in lemon grass extract were found by Suaeyun et al. (1997) to inhibit azoxymethane (AOM)-initiated colon carcinogenesis in the rat. Puatanachokchai et al. (2002) showed a similar lemon-grass extract inhibited the early stages of hepatocarcinogenesis in diethyl-nitrosamine (DEN)-treated male Fischer 344 rats by reducing the number of putatively preneoplastic, glutathione S-transferase placental form-positive lesions, as well as the level of oxidative hepatocyte nuclear DNA injury, assessed by 8-hydroxyguanosine production.

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Lentils (*Lens culinaris* L.)

Legume seeds such as lentils provide an inexpensive source of protein for a large part of the world's population. Like other legumes, lentils contain phytohemagglutinins and protease inhibitors, which must be destroyed by cooking before they can be utilized in the diet. Duenas and coworkers (2003) identified proanthocyanidins in the seed coat of lentils. The major monomeric flavan-3-ol identified was (+) catechin-3-glucose followed by smaller amounts of (+)-catechin and (–)-epicatechin. The latter compounds were reported to exhibit potent antioxidant and freeradical-scavenging activities and to inhibit platelet aggregation and antiulcer activity against stomach-mucosa injury (Vinson et al., 1995; Cook and Samman, 1996; Duenas et al., 2003). The large amounts of these bioactive compounds in lentil seed coats represent a potential source of nutraceuticals

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Lettuce (*Lactuca sativa*)

Lettuce leaves are quite low in phenolic s, but Kang and Saltveit (2002) reported a fourfold increase in iceberg and romaine lettuce following heat-shock (45°C for 2.5 min. in water) treatment or wounding. This increase in phenolics was accompanied by a corresponding increase in antioxidant power (FRAP). Serafini and coworkers (2002) showed that ingestion of 260 g fresh lettuce raised the plasma-antioxidant levels in 11 healthy volunteers compared to the same lettuce stored at 5°C under modified atmosphere-packaging conditions (MAP: O₂-N₂, 5:95 v/v). Ingestion of the fresh lettuce

resulted in significantly higher plasma total radical-trapping potential (TRAP) compared to the MAP stored lettuce. In addition, there was a significant increase in plasma quercetin, p-coumaric, caffeic acid, β -carotene, and vitamin C following consumption of fresh lettuce, which was not observed following ingestion of MAP lettuce. Thus, optimized MAP storage conditions were needed to better preserve the bioactive components of fresh-cut produce.

Nicolle and coworkers (2004) recently found male Wistar rats fed a diet containing 20 percent freeze-dried lettuce over a three-week period had increased excretion of cholesterol end products, as well as enhanced antioxidant status (Figure L.60). A slight but significant ($p<0.05$) decrease in cholesterol was observed in rats on the lettuce-fed diet, while triacylglycerol levels were unaffected. A decrease of -23 percent in cholesterol levels in the plasma triacylglycerol-rich lipoprotein (with a minor contribution of LDL) fraction was accompanied by an increase of +18 percent in the HDL fraction and a slight decrease of -7 percent in triacylglycerol levels in the lettuce-fed rats compared to the control. Nicolle and coworkers (2004) attributed these

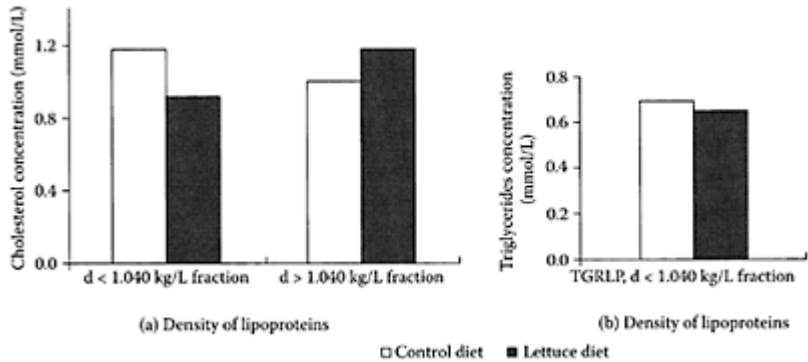


FIGURE L.60 (a) Changes in the distribution of cholesterol in the various lipoprotein fractions in rats fed control or lettuce diets. The fractions with $d<1.040$ kg/L correspond chiefly to triacycylglycerol-rich lipoproteins (TGRLP), with a lower contribution of LDL. The fractions with $d<1.040$ kg/L correspond essentially to HDL; (b) differences in the repartition of triacylglycerols in plasma-lipoprotein fractions of rats fed control or lettuce diets. Each value is the mean of triplicate analyses of a pool of eight

plasma. (Nicolle et al., *Clinical Nutr.*, 23:605–614, 2004. With permission.)

TABLE L.43
Fiber and Antioxidant Content of Lettuce¹

	Lettuce
Energy (kJ/g)	9.4
Fiber (mg/g.d.w.)	260
Vitamin C (µg/g.d.w.)	840±11
Vitamin E (µg/g.d.w.)	577±14
Lutein (µg/g.d.w.)	176±13
Nonidentified xanthophyll (µg/g.d.w.) as lutein equivalent	114±8
β-carotene (µg/d.w.w.)	66±2.3
Total phenolic compounds (mg/g.d.w.) as gallic-acid equivalent	28.5±11

¹ On a dry-weight basis. Values expressed as means of triplicate analysis ± SEM.

Source: Nicolle et al., *Clinical Nutr.*, 23:605–614, 2004. With permission.

beneficial effects to the fiber and antioxidant content of lettuce (Table L.43).

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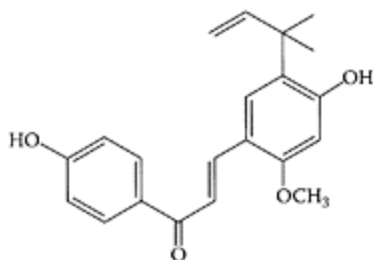
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Licochalcone A

Licochalcone A is an oxygenated chalcone first isolated from Chinese licorice roots, which has considerable biological activity (Nadelmann et al., 1997). Barfod and coworkers (2002) found licochalcone A and



Licochalcone A. (From Fukai et al., *Fitoterapia*, 74:720–724, 2003. With permission.)

four synthetic analogues inhibited proliferation of lymphocytes, as well as the production of proinflammatory and anti-inflammatory cytokines. These results suggested that these compounds exert immunomodulatory effects, which may be useful for treating some diseases. Oral administration of licochalcone A (30 mg/kg/day) to mice with glomerular disease (Masugi-nephritis) was found by Fukai et al. (2003) to reduce the urinary-protein excretion compared to nephritic mice. Licochalcone A also exhibited weak scavenging activity against superoxide radicals.

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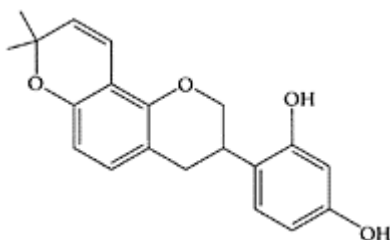
Licorice

see also Glabridin, Glycyrrhin, and Glycyrrhizic acid Licorice root, one of the oldest and most commonly used botanicals in Chinese medicine, has been used worldwide for medicinal purposes since ancient times (Liu et al., 2000). The key components associated with its medicinal properties are triterpenes, polyphenols, polysaccharides, flavonoids, alkaloids, poly amines, and essential oils. Licorice triterpenes are nonsteroidal agents exhibiting both antioxidant and anti-inflammatory properties (Wang and Nixon, 2001). The most important triterpene in licorice, glycyrrhizin (GL), is hydrolyzed to its major metabolite, glycyrrhetic acid (GA) (Wang et al., 1998). GA exists in two different forms, 18 α -glycyrrhetic acid (α -GA) and 18 β -glycyrrhetic acid (β -GA), both of which

various concentrations (0–100 μM). Cells were harvested, and the incorporated radioactivity was measured with a scintillation liquid. Data are presented as percent inhibition of controls. Values are means \pm SD of three experiments. (Ofir et al., *J. Mol. Neurosci.*, 20:135–140, 2003. With permission.)

from being released from mitochondria, which is essential for cell apoptosis to occur. Thus, licorice components appear to act as chemopreventive agents with potential as new pharmaceuticals for treating cancers.

Ofir and coworkers (2003) recently showed that licorice isoflavans and isoflavene were capable of inhibiting serotonin re-up, a known pharmacological treatment for major depression, as well as anxiety, appetite, and obsessive-compulsive disorders (Barker and Blakely, 1995). Glabridin, for example, mimicked estradiol by



Glabridin. (Adapted from Tamir et al., *J. Steroid Biochem. Mol. Biol.*, 78:291–298, 2001.)

inhibiting serotonin reuptake in a dose-dependent manner (Figure L.61). The ability to inhibit serotonin reuptake was facilitated by the lipophilic part of the isoflavans, as well as the hydroxyl at position 2' in the B ring. These licorice constituents appear to have considerable potential for the therapeutic treatment of mild to moderate depression in premenopausal and postmenopausal women.

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Lignans

see also Flaxseed, Matairesinol, and Secoisolariciresinol Lignans are a complex group of phenolic compounds widely distributed in the plant kingdom, composed of phenylpropane dimers linked by β – β bonds with a 1,4-diarylbutane structure (Smeds and Hakala, 2003). Flaxseed is the richest source of lignans compared to other food sources, such as soybean, oat bran, and lentils, as summarized in Table L.44. The main lignan precursors in flaxseed are Secoisolariciresinol (SEC) and matairesinol (MAT) (Scheme L.36). SEC is normally present in the form of Secoisolariciresinol diglucoside (SDG), which is converted by bacteria in the gastrointestinal tract to enterodiol and enterolactone. Both enterodiol and enterolactone were shown to inhibit the growth of human colon-cancer cells at a concentration of 100 μ mM (Sung et al., 1998). Supplementation of flaxseed in the diets of rats decreased the number of aberrant crypts and foci in AOM-treated rats (Serraino and Thompson, 1992). A dose-dependent reduction in metastasis and the growth of secondary tumors observed in mice fed flaxseed by Yan et al. (1998) indicated its potential for preventing metastasis.

TABLE L.44
Level of Lignans in Some Plant Food Sources

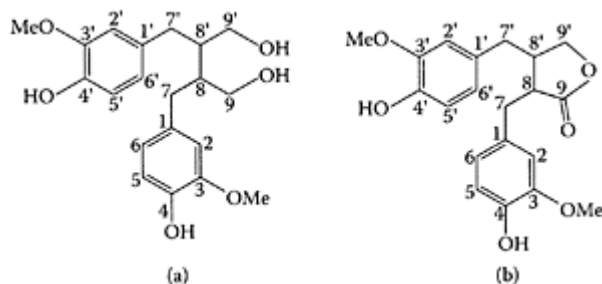
Food	Lignans (total) (ugg ⁻¹)
Flaxseed meal	675

Flaxseed flour	527
Lentils	17
Soy bean	8.6
Oat bran	6.5
Wheat bran	5.6
Kidney bean	5.6

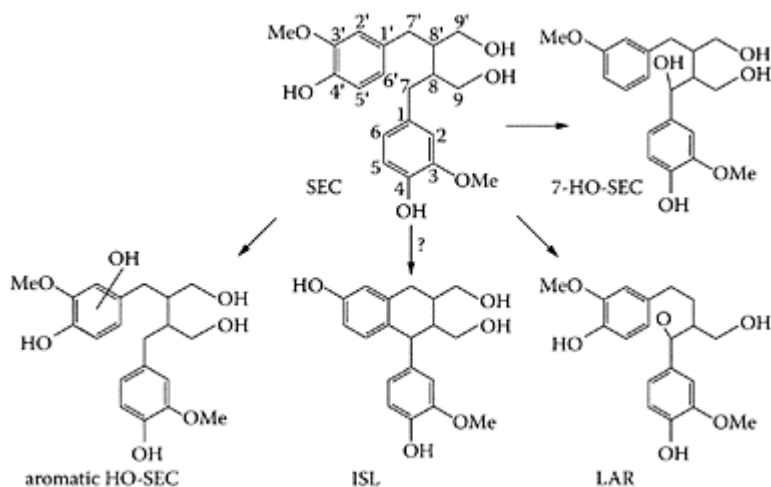
Source: Adapted from Reinli and Block, *Nutr.Cancer*, 26:123–148, 1996.

Niemeyer and Metzler (2002) examined the oxidative metabolism of lignans SEC and MAT and showed they were both excellent substrates for cytochrome P450 hydroxylation at the aliphatic and aromatic positions in the molecule. The different pathways involved are outlined in Scheme L.37. However, the genotoxic potential of these hydroxylated products, including isolariciresinol (ISL) and lariciresinol (LAR), have yet to be determined.

Owen and coworkers (2000) showed for the first time that lignans (+)-1-acetoxypinoresinol and (+)-pinoresinol were major components of the phenolic fractions in extra-virgin olive oils. They were virtually absent in the corresponding refined oils. Nurmi and coworkers (2003) reported that lignans in red wine ranged from 0.812 to 1.406 mg/L, with isolariciresinol being the main one.



SCHEME L.36 Structure and numbering of Secoisolariciresinol (a) and matairesinol (b). (From Saarinen et al., *J. Chromatogr. B.*, 777:311–319, 2002. With permission.)



SCHEME L.37 Oxidative pathways in the metabolism of SEC. (Niemeyer and Metzler, *J. Chromatogr. B.*, 777:321–327, 2002. With permission.)

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Limes (*Citrus aurantifolia*)

Limes, members of the Rutaceae family, only grow in a tropical climate. Many different varieties are cultivated in the Middle East, tropical Asia, and in Florida in the United States. Kawaii and coworkers (1999) examined the antiproliferative effects of the readily extractable fraction from 34 important citrus juices on four different human cancer cells. Of these extracts, sweet lime inhibited the proliferation of three of these lines but was much less toxic towards normal human cell

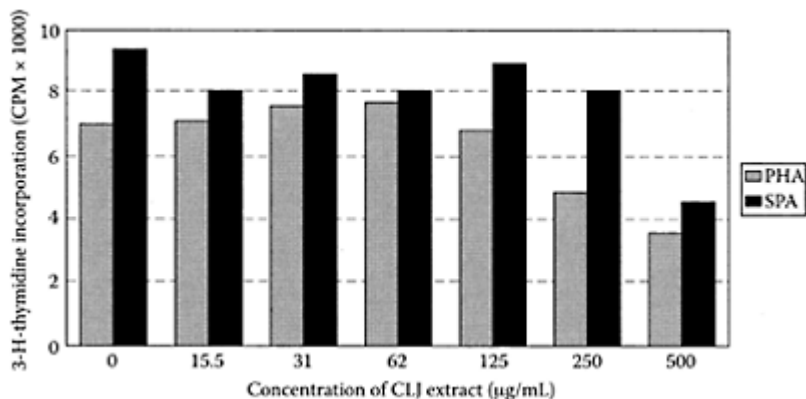
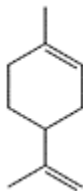


FIGURE L.62 Inhibitory effect of concentrated lime juice (CLJ) on the proliferation of PHA- and SPA-activated mononuclear cells. Proliferation of PHA-activated mononuclear cells was significantly inhibited by 250 and 500 µg/mL of CLJ extract, whereas only 500 µg/mL of the extract could induce significant inhibition in proliferation of SPA-activated mononuclear cells. Each value represents the mean \pm SD of at least three independent measurements,

$p < 0.05$ was considered significant with regard to unstimulated control (0 $\mu\text{g/mL}$ of CLJ extract). (From Gharagozloo and Ghaderi, *J. Ethnopharmacol.*, 77:85–90, 2001. With permission.)



d-Limonene. (Adapted from Casuscelli et al., *Appl. Cat., A: General*, 274:115–122, 2004.)

lines. Gharagozloo and Ghaderi (2001) later reported a concentrated lime-juice extract exhibited immunomodulatory effects on activated cultured human mononuclear cells. The levels of extract needed to inhibit proliferation of phytohemagglutinin (PHA)-activated mononuclear cells were 250 and 500 $\mu\text{g/mL}$, while inhibition of staphylococcal protein (SPA)-activated mononuclear cells required 500 $\mu\text{g/mL}$ (Figure L.62). They suggested that it was the protein components in the lime-juice extract that appeared responsible for its immunomodulatory properties.

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Limonene

d-Limonene is a monocyclic monoterpene in essential oils of citrus fruits, spices, and herbs. Orange peel is a particularly rich source, ranging from 90–95 percent (w/w). Limonene has been reported to exhibit chemoprotective activity against spontaneously and chemically induced tumors in the skin (Elegbede et al., 1988), liver (Dietrich and Swenberg, 1991), mammary gland (Elson et al., 1988; Maltzman et al., 1989), and lung and forestomach of rodents (Wattenberg et al., 1989; Watenberg and Coccia, 1991).

Kawamori et al. (1996) showed d-limonene was effective against azoxymethane (AOM)-induced colon cancer in F344 rats. Those treated with 0.5 percent *d*-limonene in the drinking water had a significantly lower number of 2, 3, and 4 crypts compared to (AOM)-treated rats (Table L.45). These researchers confirmed the ability of *d*-limonene to inhibit formation of colonic ACF by blocking formation of (AOM)-induced ACF in the colon. Uedo and coworkers (1999) examined the mechanism involved in inhibiting gastric

TABLE L.45
Effect of *d*-Limonene on Aberrant Crypt/Focus
Induced by AOM in Rat Colon¹

Treatment	ACF/Focus				
	1 crypts	2 crypts	3 crypts	4 crypts	5 crypts
AOM alone	46.0±6.6	48.5±11.7	28.8±5.4	6.6±1.1	1.5±1
AOM+ <i>d</i> -limonene	40.5±11.5	32.8±6.0 ^b	14.2±4.1 ^c	1.5±0.5 ^c	0.5±0.8

¹ Significantly different from AOM alone by Student's t test (b, *p*<0.05; c, *p*<0.001).
From Kawamori et al., *Carcinogenesis*, 17:369–372, 1996. With permission.

carcinogenesis in Wistar rats induced by *N*-methyl-*N'*-nitrosoguanidine. Feeding 2 percent limonene significantly inhibited the induced cancer through increased apoptosis and decreased DNA synthesis.

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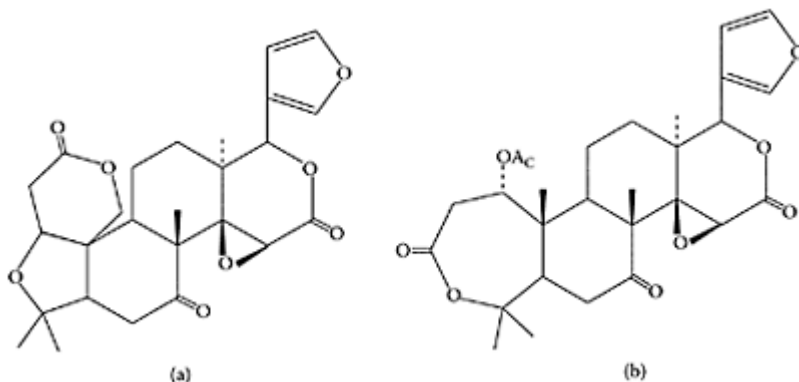
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Limonin

see also Limonoids Limonin glucoside, one of the most abundant limonoids in citrus fruit, is readily available in orange-juice and citrus-juice processing byproducts (Schoch et al., 2001; Ifuku et al., 1998). Together with nomilin, they both inhibited forestomach, buccal pouch, lung, and skin carcinogenesis in rodents (Lam et al., 1989; Wada, 1996). Tanaka and coworkers (2000) clearly demonstrated inhibition of AOM-induced colonic ACF by dietary limonin or obacunone with suppression of preneoplasia to malignancy. This was evident by significantly lower incidences of multiplicities in the treated groups compared to the AOM control (Table L.46).

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Citrus limonoids, limonin (a) and nomilin (b). (From Kelly et al., *Nutr. Res.*, 23:681–690, 2003. With permission.)

TABLE L.46
Incidence and Multiplicity of Large-Intestinal Neoplasm of Rats Fed Obacunone or Limonin (During or After Exposure to AOM)

Group No.	Treatment	No. of Rats Examined	Incidence of Rats with Neoplasm			Multiplicity (No. or Tumors/rat, Mean ± SD)		
			Total	AD ¹	ADC	Total	AD ¹	ADC
1	AOM only	25	10(75%)	2(8%)	18(72%)	0.84±0.61	0.08±0.27	0.76±0.51
2	AOM+500 ppm obacunone	16	5 ^a (31%)	1(6%)	4 ^b (25%)	0.38±0.60 ^c	0.04±0.24	0.31±0.58 ^d
3	AOM+500 ppm limonin	16	3 ^e (19%)	2(13%)	1 ^f (6%)	0.19±0.39 ^g	0.13±0.33	0.06±0.24 ^g
4	AOM+500 ppm obacunone	16	2 ^h (13%)	0(0%)	2 ^h (13%)	0.13±0.33 ^g	0	0.13±0.33 ^g
5	AOM+500 ppm limonin	16	3 ^e (19%)	1(6%)	2 ^e (13%)	0.19±0.39 ^g	0.06±0.24	0.13±0.33 ^g
6	500 ppm obacunone	8	0(0%)	0(0%)	0(0%)	0	0	0
7	500 ppm limonin	8	0(0%)	0(0%)	0(0%)	0	0	0
8	No treatment	8	0(0%)	0(0%)	0(0%)	0	0	0

¹ AD, adenoma; ADC, adenocarcinoma.

² O, obacunone; L, limonin.

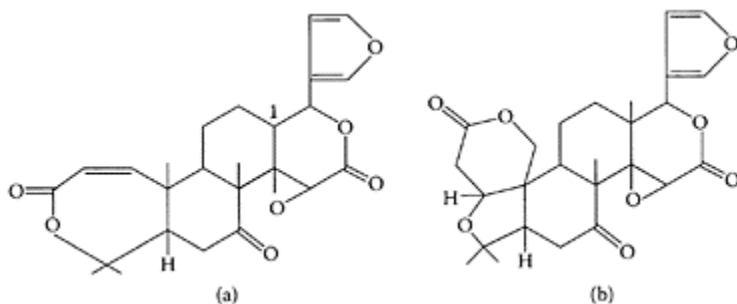
^{a-h} Statistically significant from group 1: ^a*p*=0.012; ^b*p*=0.004; ^c*p*<0.05; ^d*p*<0.02; ^e*p*=0.001; ^f*p*=0.00003; ^g*p*<0.001; ^h*p*=0.0002.

Source: Tanaka et al., *Carcinogenesis*, 22:193–198, 2001. With permission.

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SCHEME L.38 Chemical structures of (a) obacunone and (b) limonin. (Tanaka et al., *Carcinogenesis*, 22:193–198, 2000. With permission.)

Limonoids

see also Limonin Limonoids are a group of highly oxygenated triterpenoids found in members of the Rutaceae (citrus fruits) and Maliaceae (neem) families. Citrus fruits are particularly rich sources of limonoids, with the most prevalent being obacunone and limonin (Scheme L.38). They impart bitterness to citrus juices, but as the fruit matures, they form glycosides, which are tasteless and water soluble. The anticancer properties of limonoids are attributed to their induction of the phase II enzyme, glutathione S-transferase (Lam et al., 1989; Kelly et al., 2003). Administration of high doses of citrus limonoids to four groups of healthy male and female subjects were shown by Manners and coworkers (2003) to be readily bioavailable and nontoxic.

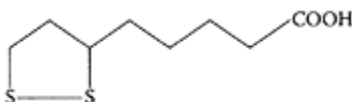
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α -Lipoic acid

α -Lipoic acid (thioctic acid), a short-chain fatty acid with two sulfur atoms, is a naturally occurring coenzyme of pyruvate and α -ketoglutarate dehydrogenases. It can be reduced to dihydrolipoic acid, with the two sulfur atoms converted to sulfhydryl groups. Lipoic acid is found mainly in meat and liver and could not be detected in vegetables (Hiroyuki, 1998). It appears to be a useful, therapeutic agent for neurological and liver disorders (Packer et al., 1995; Bustamante et al.,



α -Lipoic acid. (From Sitton et al., *J. Biochem. Biophys. Methods*, 61:119–124, 2004. With permission.)

1998). A recent study by Obrosova and coworkers (2003) confirmed the effectiveness of DL- α -lipoic acid as an antioxidant by reducing oxidative stress in rat renal cortex during early diabetes. Preclinical trials were recommended to assess the efficacy of lipoic acid for treating diabetic complications, such as diabetic nephropathy. Gibson et al. (2003) also confirmed the major role of oxidative stress in diabetic autonomic and somatic neuropathy, by the ability of α -lipoic acid to protect autonomic nerves of gastric fundus and the vascular supply of these nerves and neuronal-cell bodies from damage by reactive-oxygen species (ROS). As seen in Figure L.63, α -lipoic acid corrected the defective,

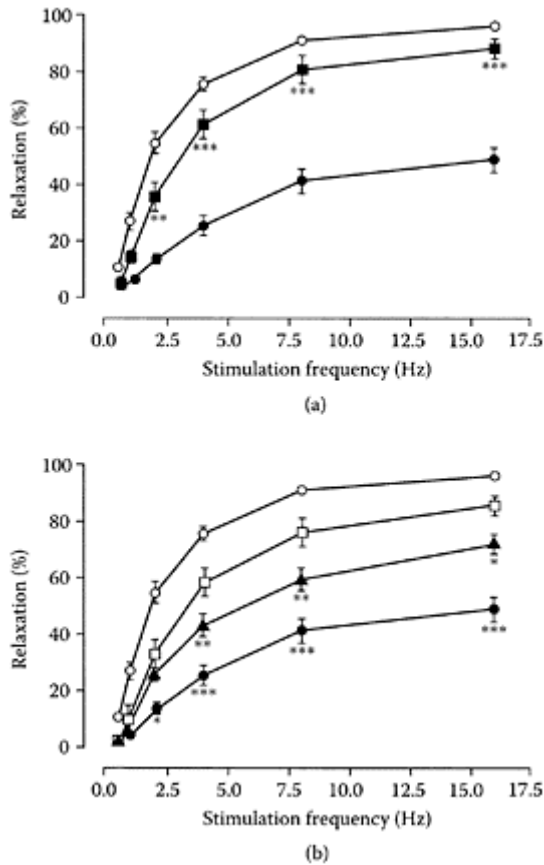


FIGURE L.63 (a,b) Effect of diabetes and chronic α -lipoic-acid treatment on NANC-mediated frequency response curves in 5-hydroxytryptamine (5-HT) precontracted rat gastric fundus longitudinal muscle strips, (a) Prevention study: nondiabetic control group, n=18. Eight-week diabetic control group, n=20; α -lipoic acid prevention treatment diabetic group, n=9. Data are mean \pm SEM. ** p <0.01, *** p < 0.001 compared to eight-week diabetic control group, (b) Intervention study: nondiabetic (○) and 8 week diabetic (●) groups.

diabetic () control groups as in (a), plotted for comparison; 4 week diabetic control group, n=17; α -lipoic acid intervention group treated for 4 weeks following 4 weeks of untreated diabetes, n=8. Data are mean \pm . * p <0.05, ** p <0.01, *** p <0.001 vs. α -lipoic acid intervention treatment group (Gibson et al., *Free Rad. Biol. Med.*, 35:160–168, 2003. With permission.)

relaxation-impaired gastric fundus nonadrenergic, noncholinergic (NANC) nerves caused by diabetes by providing 82.8 percent protection for maximum relaxation (16 Hz, p <0.001).

Lapenna et al. (2003) recently showed that it was the reduced form of lipoic acid, dihydrolipoic acid, not lipoic acid, that inhibited 15-lipoxygenase-dependent lipid peroxidation, suggesting possible antioxidant and antiathrogenic properties.

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Lipoproteins

Lipoproteins are conjugated proteins in which simple proteins are combined with lipid components, such as cholesterol or triacylglycerols. They are classified according to their density as low-density (LDL) or high-density (HDL) lipoproteins. LDL and HDL both transport lipids in the watery fluids of the body; however, HDL transports cholesterol from the peripheral tissues to the liver for oxidation. High LDL and low HDL levels are associated with a high risk of ischemic heart disease (Gordon and Rifkind, 1989). However, a high level of HDL cholesterol appears to protect the arterial wall from the formation of atherosclerotic lesions by removing lipids (Yancey et al., 2003).

The protective effect afforded by HDL against ischemic heart disease appears to be mediated via a reduced cardiac tumor necrosis factor- α (TNF- α) content and enhanced cardiac prostaglandin release (Calabresi et al., 2003). Apolipoprotein-specific synthetic HDLs made by combining phosphatidylcholine and apolipoprotein A-1 were proposed by Sirtori et al. (1999) as novel, therapeutic tools for treating cardiovascular diseases. They reported that it was possible to produce synthetic HDLs on a large scale and to safely administer high doses to humans. Subsequent research showed the effectiveness of these synthetic HDLs in animal models of atherosclerosis, arterial thrombosis, and hemorrhagic and septic shock (Sha et al., 2001; Cockerill et al., 2001; Chiesa et al., 2002). Rossoni et al. (2004) demonstrated the cardioprotective effects of administering synthetic HDLs to isolated rat hearts 10 min prior to ischemia by the rapid and dose-dependent improvement in postischemic cardiac function. The left ventricular developed pressure recovered to 71 ± 3.2 compared to 40.5 ± 3.8 mm Hg for the saline-treated hearts, while cardiac perfusion pressure increased to 100.3 ± 6.2 compared to 132.0 ± 9.0 mm Hg.

LDL cholesterol, because of its detrimental relationship to cardiovascular disease, cannot be considered a nutraceutical. Nevertheless, the oxidized form of this low-density lipoprotein (OxLDLs) appears to function as a specific delivery system for photosensitizers to the scavenger receptors expressed on the macrophages in atherosclerotic lesions, enhancing the benefits of photodynamic therapy (De Vries et al., 1999). Photodynamic therapy, a promising new therapy for cardiovascular pathologies, such as atherosclerosis and retinopathy, involves the specific delivery of a photosensitizer, such as aluminum phthalocyanine chloride (AlPc), to the atherosclerotic plaque, where it is activated by light of a specific wavelength, reducing the narrowing of the artery (Nyamkeye et al., 1996).

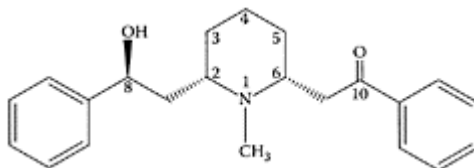
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Lobeline

Lobeline, an alkaloid constituent of Indian tobacco (*Lobelia inflata*), is a nicotine antagonist and may be useful as a smoking cessation agent. A clinical trial by Schneider and Olsson (1996) found that treatment with 7.5 mg lobeline resulted in a sustained abstinence from tobacco over the last four weeks of the study in 10 out of 34 treated subjects compared to 8 out of 47 subjects on the placebo. A multicenter study of sublingual lobeline tablet use and cessation of smoking with 750 subjects by Glover



Lobeline. (From Dwoskin and Crooks, *Biochem. Pharmacol.*, 63:89–98, 2002. With permission.)

and coworkers (1998) found no statistical differences between lobeline and the placebo. In one of three sites, however, there was significant efficacy so that lobeline as a smoking cessation agent still remains controversial. The ability of lobeline to inhibit amphetamine-induced release of dopamine *in vitro* and amphetamine-induced hyperactivity suggested to Dwoskin and Crooks (2002) that lobeline and its analogues could act as therapeutic agents for treating methamphetamine abuse. The potential of lobeline as a novel pharmacotherapy for treating psychostimulant abuse was further confirmed by Miller and coworkers (2003), who showed lobeline attenuated locomotor stimulation in rats induced by the repeated nicotine administration.

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Lovage (*Levisticum officinale* Koch.)

Lovage, a member of the *Apiaceae* family, is an aromatic and perennial medicinal herb grown extensively in Europe. The name is derived from its reputation as a love charm or aphrodisiac (Stuart, 1989). The essential oil from its leaves, seeds, and roots is used in food, beverages, and perfumery (Cu et al., 1990). Of 191 compounds identified in the oil, Toulemonde and Noleau (1988) showed that β -phellandrene accounted for 63 percent of the seed oil, while n-butylidene-4,5-dihydrophthalide was the major constituent in root oil (67 percent). Bylaite and coworkers (1998) showed that lovage seeds and flowers were the richest sources of oil with α -terpinyl acetate, the major constituent in the leaves and stems (up to 70 percent), while β -phellandrene accounted for 61.5 percent and 40.8 percent of the seed and flower oils, respectively. They also identified Z-ligustilide as a major phthalide in lovage leaves and stem oils, ranging from 4.4 percent–11.7 percent and 4.8–13.8 percent, respectively, depending on the harvesting time. Later work by Bylaite and coworkers (2000), using dynamic headspace gas chromatography and olfactometry analysis, showed that while β -phellandrene was the dominant constituent in lovage oil, its impact on aroma was not the most significant.

The medicinal properties of lovage can be traced back to the Benedictine monks who recommended chewing the seed to aid digestion and relieve flatulence (Stuart, 1989). Lovage roots were also known for centuries to possess carminative and spasmolytic

activity (Segebrecht and Schilcher, 1989). Its use as a folk medicine in Europe is related to its calming effect on the stomach, as well as in the treatment of congestion, rheumatism, and migraine headaches. It was approved in Germany for inflamed urinary tract and preventing kidney stones (Hogg et al, 2001). Excessive dosages of lovage should be avoided by pregnant women, as it promotes the onset of menstruation, while its irritant action can cause kidney damage (Maybe et al., 1988; Stuart, 1989)

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Low-density lipoprotein

see Lipoproteins

Lunasin

Lunasin, a soybean peptide consisting of 43 amino acids, contains at the carboxyl end none Asp(D) residues, an Arg-Gly-Arg (RGD) cell adhesion motif, and a predicted helix with structural homology to a conserved region of chromatin-binding proteins. Galvez

and de Lumen (1999) reported that transfection of mammalian cells with the lunasin gene arrested mitosis, resulting in cell death. Galvez et al. (2001) further confirmed the chemopreventive properties of soybean lunasin by its ability to induce apoptosis in the SENCAR mouse-skin cancer model. Application of lunasin (250 µg/week) reduced skin-tumor incidence/mouse by 70 percent, as well as delayed the appearance of tumors by two weeks compared to the control. The antitumor activity of lunasin action resulted from its ability to prevent histone acetylation by binding preferentially to deacetylated histone H4 *in vitro*. Jeong and coworkers (2003) showed the feasibility of large-scale production of soybean lunasin capable of suppressing the formation of mammalian cells by an oncogene.

Using Western blot analysis, Jeong et al. (2002) isolated and purified a lunasin peptide from barley. Different barley lunasin fractions

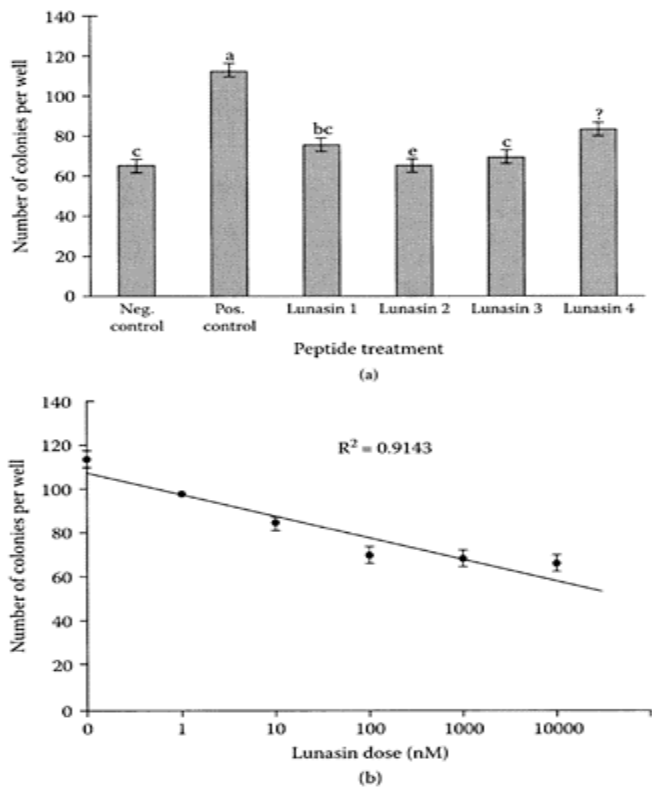


FIGURE L.64 Purified lunasin inhibits colony formation in IPTG-induced *ras* stably transformed 2-12 cells, (a) At a concentration of 10 µM, barley lunasin purified using different methods was as effective in inhibiting

colony formation as synthetic lunasin. Negative control was not treated with IPTG, while positive control was treated with IPTG without lunasin. Lunasin 1 is the crude extract of barley lunasin; lunasin 2 is lunasin 1 purified by ion-exchange chromatography by elution at 0.7 M NaCl and not dialyzed before bioassay; lunasin 3 is lunasin 2 purified by immunoaffinity chromatography; and lunasin 4 is synthetic lunasin. Treatment means (\pm standard errors) with similar letters are not significantly different from each other, as analyzed by a OneWay ANOVA followed by Duncan's Multiple Range Test, (b) Dose response of immuno-purified barley lunasin fraction in suppression of colony formation. Each lunasin dose represents the means (\pm standard error) of triplicate experiments. (Jeong et al., *J. Agric. Food Chem.*, 50:5903–5908, 2002. With permission)

were shown to inhibit colony formation in isopropyl- β -D-thiogalactoside (IPTG)-induced, ras-stably infected mouse-fibroblast cells as effectively as a chemically synthesized lunasin at a concentration of 10 μ M (Figure L.64). These fractions also inhibited histone acetylation, attributed previously to the antitumor properties of soybean lunasin. Identification of lunasin in barley suggests it could be present in other plant seeds.

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Lutein

Lutein is a 40-carbon hydroxylated carotenoid or xanthophyll yellow pigment in dark-green vegetables, as well as in egg yolk, corn, orange juice, melon, and orange peppers masked by chlorophyll (Pfander, 1992; Sommerburg et al., 1998). It is found, together with zeaxanthin, in large concentrations in the area of the human retina involved in central vision, known as macula lutea.

Both of these pigments are implicated in the pathogenesis of macular degeneration, a condition leading to loss of vision in the elderly (Seddon et al., 1994).

Epidemiological evidence pointed to an association between macular degeneration and carotenoid intake. The concentration of lutein and zeaxanthin were significantly lower in eyes suffering from macular degeneration compared to healthy controls (Beatty et al., 2001). Researchers at the University of Pennsylvania showed that supplementation of lutein by patients suffering from choroideremia, a genetically linked retinal disease, significantly increased the macular optical density (Duncan et al., 2002). A 50 percent increase in macular pigment optical density was also reported by Richer and coworkers (2002), which further established the role of lutein in improving visual function in patients suffering from age-related macular degeneration. Semba and Dagnelie (2003) concluded that lutein and zeaxanthin acted as antioxidants reducing photo-oxidative stress in the retina by deactivating highly reactive singlet oxygen $^1\text{O}_2$. A two-year, double-blind, placebo-controlled study by Olmedilla and coworkers (2003) showed that only supplementation with lutein improved visual acuity of patients with age-related cataracts compared to α -tocopherol and the placebo (Figure L.65). These results suggested that long-term supplementation with lutein could be beneficial to individuals suffering from age-related cataracts.

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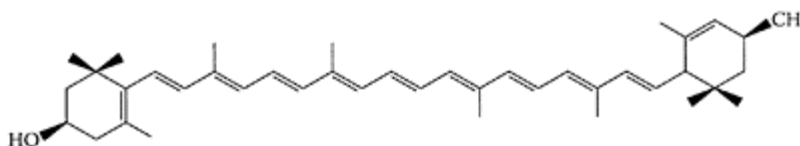
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Lutein. (Adapted from Alves-Rodrigues and Shao, *Toxicol. Lett.*, 150:57–83, 2004.)

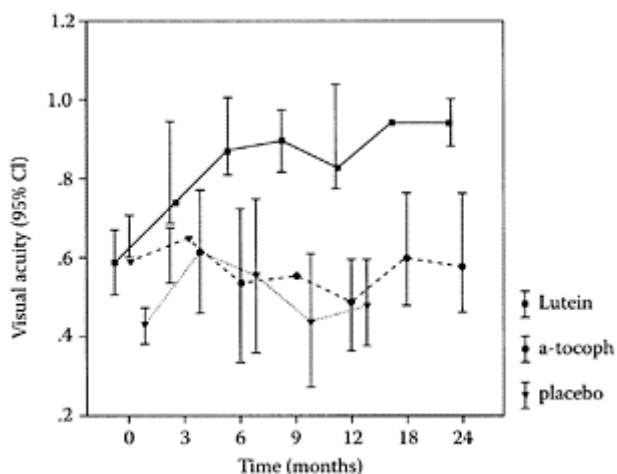


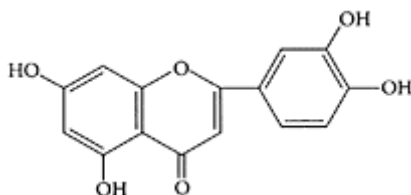
FIGURE L.65 Changes in visual acuity of patients with cataracts during supplementation study (eyes were assessed individually). Lutein group (n=9), α -tocopherol (n=10), and placebo group (n=7), CI, confidence interval. (Olmedilla et al., *Nutrition*, 19:21–24, 2003. With permission.)

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Luteolin

Luteolin, a 3', 4', 5,7-tetrahydroxyflavone, is found in the glycosylated form in celery, green pepper, perilla leaf, and chamomile tea (Shimoi et al., 1998). It has been shown to exhibit antimutagenic, antitumorigenic, antioxidant, and anti-inflammatory properties (Samejima et al., 1995; Kim et al., 1999; Casagrande and Darbon, 2001; Xagorari et al., 2001). Casagrande and Darbon (2003) found luteolin was a potent inhibitor of lipopolysaccharide (LPS)-stimulated nuclear factor-kappa B (NF-κB) transcriptional activity in Rat-1



Luteolin. (From Li et al., *J. Pharm. Biomed. Anal.*, 37:615–620, 2005. With permission.)

fibroblasts by modulating the transcription complex assembly in the fibroblasts. Miagkov et al. (1998) showed NF-κB played a critical role in chronic inflammation.

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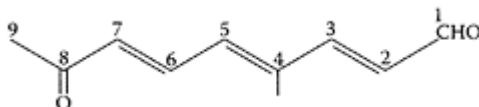
Lycopene

Lycopene is an acyclic isomer of the carotenoid β -carotene without any vitamin A activity (Stahl and Sies, 1996). It is found in abundance in fresh, ripe tomatoes and to a lesser extent in watermelon, papaya, guava, and grapefruit. Structurally, lycopene is a highly unsaturated, straight-chain hydrocarbon in which 11 of its 13 double bonds are conjugated (Argawal and Rao, 2000). It occurs predominantly in the *trans* isomer but undergoes isomerization to the *cis* isomer during heat processing. In fact, the increased levels of the *cis* isomer accounts for the much greater absorption of lycopene in processed tomato products (Stahl and Sies, 1992). Lycopene is a potent antioxidant with singlet oxygen-quenching ability twice that of β -carotene and 10 times that of α -tocopherol and is also able to inactivate hydrogen peroxide and nitrogen dioxide (Bohm et al, 2001; Heber and Lu, 2002).

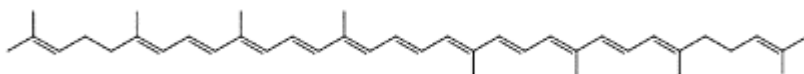
Epidemiological studies showed that diets supplemented with lycopene reduced the risk of many chronic diseases, such as cancer and heart disease (Edward, 1999). The benefits associated with lycopene are related to its potent antioxidant properties through its ability to scavenge free radicals (Mortensen et al., 1997). Porrini and Riso (2000) showed that a daily consumption of 25 grams of tomato paste by healthy young women significantly increased plasma and lymphocyte lycopene concentrations after 14 days. Exposure of collected blood lymphocyte samples to free radicals using the Comet Test showed a significant reduction of 50 percent DNA damage compared to the control samples. A further study by Chen and associates (2001) showed that dietary lycopene fed to men with prostate cancer significantly reduced hydroxylated guanosine (8-OHdG), a by-product and useful biomarker of oxidative DNA damage in cell nuclei, by 21.3 percent. This indicated that lycopene exerted a protective effect on white blood cells by reducing oxidative damage in cancerous prostate tissue. Bowen and coworkers (2002) showed that consumption of tomato-sauce dishes containing 30 mg of lycopene per day for three weeks by 22 patients with localized prostate adenocarcinoma significantly reduced serum-prostate-specific antigen (PSA) levels and DNA oxidation. A recent examination of patients undergoing colonoscopy for colorectal adenomas by Erhardt et

al. (2003) showed plasma lycopene concentrations were inversely related to adenoma risk, further supporting the protective role of lycopene against colorectal cancer.

Nara and coworkers (2001) reported that only when HL-60 human promyelocytic leukemia cells were exposed to an autoxidized mixture of lycopene (6 μM) for five days did they undergo apoptosis. Zhang et al. (2003) subsequently identified an oxidized cleavage product of lycopene, (E,E,E)-4-methyl-8-oxo-2,4,6-nonatrienal (MON), which they found induced



(E,E,E)-4-methyl-8-oxo-2,4,6-nonatrienal (MON). (From Zhang et al., *Free Rad. Biol. Med.*, 35:1653–1663, 2003. With permission.)



Lycopene. (Adapted from Alves-Rodrigues, A. and Shao, A., *Toxicol. Lett.*, 150:57–83, 2004.)

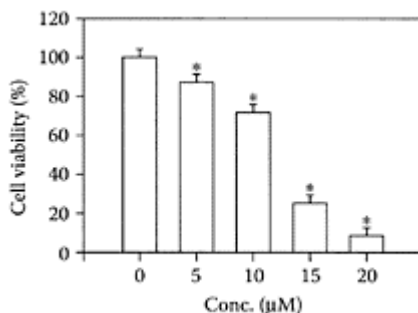


FIGURE L.66 Effect of (E,E,E)-4-methyl-8-oxo-2,4,6-nonatrienal on the viability of HL-60 cells. The cell viability was evaluated by the MTT method and is expressed as the percentage of the value of the control culture treated with the vehicle (THF) alone. Values represent means \pm SD of eight wells. The asterisk indicates a value significantly different from the vehicle value ($p < 0.01$). Statistical

comparisons were made by the Scheff's F-test. (Zhang et al., *Free Rad. Biol. Med.*, 35:1653–1663, 2003.)

DNA fragmentation and apoptosis in a time-and dose-dependent manner. Cell viability was reduced to 71.6 percent of the control in the presence of 10 μ M MON (Figure L.66).

Lycopene can also prevent cardiovascular disease. Supplementing the diet of six healthy human subjects with 60 mg/day of lycopene for three months significantly reduced their plasma LDL cholesterol levels by 14 percent (Furhman et al., 1997). Treatment of hypertensive patients with 15 mg per day of lycopene in the form of a capsule was found by Paran and Engelhard (2001) to reduce systolic blood pressure by almost 100 mm Hg over an eight-week period. Mohanty et al. (2002) also found that lycopene protected the human lens from oxidative damage and had potential as an anticataract agent.

Lycopene's potent antioxidant property could provide a treatment for neurodegenerative diseases. A recent study by Sukanuma and coworkers (2003) found dietary lycopene attenuated the age-related learning in senescenceaccelerated mice (SAMPS) by ameliorating the memory deficits in these animals. A recent review of lycopene and human health by Rao and Rao (2003) is recommended.

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Lysine

The essential amino acid, L-lysine, has been used for many years as its monohydrochloride salt (LMH) to improve the diets of many Third World countries (Flodin, 1993). Research in the 1970s suggested that oral supplements of lysine monohydrochloride suppressed recurrent herpes simplex infections (Griffith et al., 1978). As a result, pharmaceutical-grade LMH supplements are readily available in 500-mg tablets. An excellent review of the pharmacology and toxicology of lysine was published by Flodin (1997). Sarubin (2003) suggested that daily supplements of up to 3 grams of lysine appear to be safe. However, Marcason (2003) cautioned that diets high in lysine or with high lysine:arginine ratios were found to be hypercholesterolemic in some animal studies.

Poly-L-lysine has also been shown to inhibit the herpes simplex virus type 1 (HSV) by possibly preventing its adsorption (Langeland et al., 1988; WuDunn and Spear, 1989). Egal and coworkers (1999) found that magainins, a class of cationic peptides rich in lysine and octanoyl groups originally isolated from the skin of the African clawed frog (*Xenopus laevis*), had a direct antiviral effect on HSV.

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Maca

References

- # Macrolactin A

Macrolactin A. (From Barmann et al., *Tetrahedron*, 56:2283–2295, 2000. With permission.)

exhibit significant antiviral and anticancer properties, including inhibition of B16-F10 murine melanoma cells (Rychonovsky et al., 1992). The lack of an adequate supply of macrolactin for therapeutic purposes has resulted in attempts to synthesize macrolactin A and analogues (Marino et al., 2002; Kobayashi et al., 2004).

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Madonna lily (*Lilium candidum*)

Madonna lily, known by the botanical name *Lilium candidum*, belongs to the N.O. *Lililaceae* family, which grows throughout Europe. In the early days of Christianity, it was dedicated by the church to the Madonna (hence, its popular name), probably because its delicate whiteness was considered a symbol of purity. It produces stiff, erect stems, 3–5 feet high, clothed with lance-shaped leaves. The white, bowl-shaped flowers appear in June, flowering into July, and have a strong, sweet, penetrating perfume. The bulbs were long known for their therapeutic effects. They have highly demulcent and also somewhat astringent properties. They were reported as effective medicinal materials for the external treatment of burns and swellings and as emollient cataplasms for tumors, ulcers, and external inflammation. The fresh bulb, bruised and applied to hard tumors, can often ripen them in quite a short time. Antiyeast activity was observed by Mucaji et al. (2002), while the use of *Lilium candidum* bulbs as an antiviral agent to treat shingles (*Herpes zoster*) was reported by Pieroni (2000). Spirostanol saponins and jatropham isolated from the ethanolic extract of *Lilium candidum* proved potent inhibitors (>60 percent) of 12-O-tetradecanoyl-phorbol-13-acetate, a specific tumor promoter for an epidermal carcinogenesis, and in the presence of a polyaromatic carcinogenic substance 7,12-dimethylbenz(a)-anthracene (Vachalkova et al., 2000). Phytochemical studies on *Lilium candidum* demonstrated the existence of dimeric pyrroline derivatives, 3-

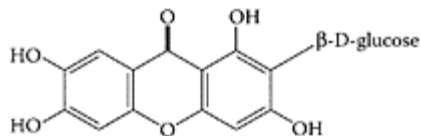
methysuccinoyl-flavone, pyrrilidineylflavone, steroidal saponins (Eisenreichova et al., 2000; Mimaki et al., 1993, 1998), and sterols (Mucaji et al., 2000). Spirostanol and furostanol saponins had inhibitory effects on Na⁺/K⁺ ATPase (Mimaki et al., 1999) and etioline, a steroidal alkaloid (Erdogan et al., 2001).

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Mangiferin

Mangiferin, 1,3,6,7-tetrahydroxyxanthone-C2- β -D-glucoside, found in higher plants, such as the stem bark of *Mangifera indica* L., is a constituent of folk medicines. It has attracted considerable attention because it is pharmacologically active, exhibiting antitumor and antiviral (Guha et al., 1996; Yoosook et al., 2000), antidiabetic (Ichiki et al., 1998; Miura et al., 2001), antbone resorption (Li et al., 1998), and antioxidant properties (Sanches et al., 2000). Yoshimi et al. (2001) showed 0.1 percent mangiferin significantly inhibited the development of aberrant crypt foci (ACF) in azoxymethane-induced tumorigenesis in F344 rats. Leiro and coworkers (2003) reported



Structure of mangiferin. (From Yoshimi et al., *Cancer Lett.*, 163:163–170, 2001. With permission.)

TABLE M.47

Effect of Mangiferin Given Intraperitoneally Daily for 28 Days on Erythrocyte MDA, CAT, and SOD in STZ-Induced Diabetic Rats

Treatment	Erythrocyte		
	nM of MDA/mL Packed RBC	CAT ($\times 10^3$) ^a U	SOD (U)
Normal rats	5.86 \pm 0.06	6.06 \pm 1.15	81.00 \pm 7.15
Negative results	0.43 \pm 0.76	3.46 \pm 0.49	52.10 \pm 13.59
Insulin (6 UI/kg)	5.93 \pm 0.51*	4.90 \pm 1.22	73.51 \pm 16.57
Mangiferin (10 mg/kg)	5.43 \pm 1.06*	4.28 \pm 1.32	65.86 \pm 8.97
Mangiferin (20 mg/kg)	5.74 \pm 0.86*	3.92 \pm 0.38	82.54 \pm 10.46

U-one unit of SOD is the amount (in :g) of protein required to inhibit MTT reduction by 50%. Values are means \pm SE of six animals.

* $p < 0.05$ as compared to negative control.

^aU-velocity constant/s

Source: From Muruganandan et al., *Toxicology*, 176:165–173, 2002. With permission.

mangiferin was a potent antioxidant that scavenged superoxide ions. Mangiferin also modulated gene expression of iNOS and cytokines, which regulate macrophage activity and participate in the regulation of NOS production, such as TNF- α and TNF- β . Thus, mangiferin may be useful for the treatment of inflammatory diseases, atherosclerosis, or septic shock. Stimulation of TNF- β , a cytokine inhibitor of angiogenesis (Mandriota et al., 1996), could also provide a useful treatment for blocking tumor growth or protect against autoimmune diseases. Garrido et al. (2004) reported, for the first time, inhibition of TNF- α and NO production by an aqueous extract of *Mangiferin indica* L. against endotoxic septic shock and microglia in rats.

A protective effect was also exerted by mangiferin in streptozotocin-induced oxidative damage to cardiac and renal tissues in rats (Muruganandan et al., 2002). This was evident by a decrease in renal and erythrocyte malondialdehyde (MDA) and catalase (CAT) and an increase in superoxide dismutase (SOD) in rats fed mangiferin intraperitoneally daily for 28 days (Table M.47).

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Mangoes

see also Maginiferin Mangoes (*Mangifera indica* L.) belong to the family *Anacardiaceae*, order *Rutales*. They grow naturally or are cultivated mainly in tropical and subtropical regions and are deeply entrenched in Indian history. Mangoes were mentioned in early Arian literature, with Alexander the Great seeing his first in 326 BC when he traveled with his army to India. Every part of the mango is used in India. The dry twigs are used in sacrificial fires for religious ceremonies, while oil is extracted from the leaves and mixed with lime juice to treat skin ailments. Smoke from burning mango leaves are used as a cure for hiccups and sore throats; kernels are dried, ground,

and used as a cure for asthma, while mango pulp is used to nurse cholera patients back to health. Dried mango flowers, containing 15 percent tannin, serve as an astringent in cases of diarrhea, chronic dysentery, catarrh of the bladder, and chronic urethritis resulting from gonorrhea. The bark contains mangiferin, polyphenols, terpenoids, steroids, fatty acids, and microelements and is astringent and employed against rheumatism and diphtheria. The resinous gum from the trunk is applied on cracks in the skin of the feet and on scabs, and is believed to be helpful in cases of syphilis.

Mangoes are an ideal summer food, as they are high in carotenoids, especially β -carotene, as well as other organic acids, such as citric acid, together with smaller amounts of shikimic, malic, and quinic acids. The sugar content varies, particularly among treatments during the storage period, although sucrose is the major sugar present in mangoes, followed by fructose and glucose (Gonzalez-Aguilar et al., 2000). Terpenes accounted for the majority of the volatile aroma components in mangoes (Macleod, 1984), while the main antioxidants are vitamins C, E, and selenium. Clinical studies showed the benefits of the high carotenoid levels in mangoes to eye health by their ability to prevent sties, corneal ulcers, and night blindness (Carlier et al., 1992; Christian et al., 1998). Extremely wide, seasonal variations in plasma ascorbic-acid levels associated with the consumption of mangoes is well known. For example, one of the first studies observed pregnant and lactating women in Keneba and Manduar, two neighboring, rural Gambian villages, showed ascorbic-acid levels peaked during the mango season in May and June, attaining a mean level of 1.4 mg/dL. The lowest levels, average 0.2 mg/dL, were observed during the rainy season in September and October (Bates et al., 1982).

The average mango (± 350 g) contains 13,615 IU β -carotene (Puerto Rican analyses of 30 cultivars showed β -carotene ranged from a low of 4,171 IU/100 g in>Stringless Peach= to a high of 7,900 IU in>Carrie), 95 mg vitamin C (ascorbic acid ranged from 3.43 mg/100 g in>Keitt=to 62.96 in>Julie), and about 3.5 mg vitamin E. The mango fruit also contains B complex vitamins and minerals, such as iron, calcium (14 mg/100 g), magnesium, potassium, phosphorus, selenium, and zinc. The carotenoid composition of mango is affected by ripening, cultivar differences, and processing. Ripening affects the major carotenoids, violaxanthin and β -carotene. All *trans*- β -carotene, all *trans*-violaxanthin, and 9-cis-violaxanthin increased in the ripe fruit in comparison to the mature green fruits. Geographic effects also appeared to be substantial. In commercially processed mango juice, violaxanthin was not detected, while auroxanthin was present at appreciable levels, with β -carotene the main carotenoid (Mercadante and Rodriguez-Amaya, 1998). Mango seed kernel is a good source of fat (5–10 percent) (Lakshminarayana et al., 1983; Asad and Bukhari, 1996), protein (7 percent), and macronutrients, Ca (15–45 mg/100 g), Na (237–239 mg/100 g), and P (31–92 mg/100 g). It was reported to enhance the oxidative stability of clarified butter, ghee (Parmar and Sharma,

1986). Recently, antimicrobial activity of the ethanol extract of mango seed kernel against foodborne, pathogenic bacteria was demonstrated (Kabuki et al., 1997). The antioxidant activity of a high-dietary-fiber mango-peel product was also recently reported (Larrauri et al., 1997).

Mango dermatitis is a common term given to allergic contact dermatitis associated with the sap or skin of the fruit *Mangifera indica*. Patch testing with diluted sap (known to contain mangiferin, resinous acid, mangiferic acid, and the resinol, mangiferol),

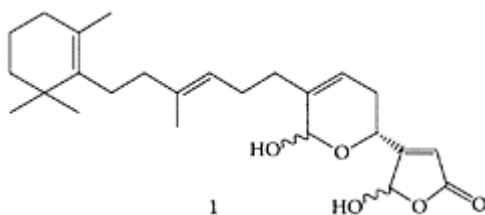
crushed leaf, crushed stem, and fruit skin is usually positive in these cases (Calvert et al., 1996).

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Manoalide

Manoalide(1), a sesquiterpenoid metabolite from the Pacific sponge *Luffariella variabilis*, is a potent analgesic and anti-inflammatory agent isolated in 1980 (De Silva and Scheuer, 1980; de Freitas et al., 1984). The antiinflammatory activity of manoalide is due to



Structure of manoalide. (From De Rosa et al., *Tetrahedron*, 56:2095–2102, 2000. With permission.)

inhibition of phospholipase A₂ (PLA₂) a hydrolytic enzyme catalysing the release of arachidonic acid from membrane-bound phospholipids. This reaction initiates a complex cascade of biochemical reactions, leading to the formation of proinflammatory mediators, such as leukotrienes and prostaglandins. Thus, it is a key therapeutic target for the suppression of inflammation and pain (Mayer et al., 1988). Manoalide has long been known as a potent and irreversible inhibitor of PLA₂ from the venoms of different species, such as cobra, bee, and rattlesnake (Lombardo and Dennis, 1985; Reynolds et al., 1991). Structure-activity relationship studies suggest that the closed-ring form of manoalide is the predominant molecular species that accounts for the selective and potent inhibition of PLA₂ (Glaser et al., 1988). The stereoselective synthesis of manoalide was carried out for the first time by Soriente et al. (1999a). Pretreatment with manoalide was found to significantly inhibit PLA₂ activity in the synovial fluid, prevent loss of proteoglycan from the condylar cartilage, and reduce proteoglycan levels in the lavage fluids, which suggested manoalide may be an effective antiarthritic agent (Schrier et al., 1996). Manoalide was also reported to inhibit superoxide release in the pathogenesis of LPS hepatotoxicity (Mayer and Spitzer, 1993). As an inhibitor of the major enzyme phospholipase A, known to be involved in different inflammatory mechanisms, manoalide was broadly studied as an antiinflammatory agent (Mayer et al., 1988; Soriente et al., 1999b). The synthesis of potentially anti-inflammatory manoalide hybrid was recently reported by Izzo et al. (2004).

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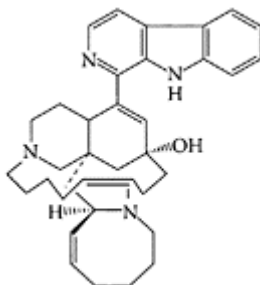
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Manzamine A

Manzamine A is an alkaloid isolated from the Okinawan marine sponge, genus *Haliclona* (Sakai et al., 1986). It consists of a complex pentacyclic-ring system with a pendant β -carboline moiety.

Many related alkaloids of the manzamine family have since been isolated from different sponge genera (Edrada et al., 1996; Tsuda et al., 1997; Magnier et al., 1998; Watanabe et al., 1998; Urban et al., 2000; Sayed et al., 2001). Manzamine A was initially described as an antitumor agent against mouse leukemia cells (Sakai et al., 1986), and recently was shown to be an antimalarial agent against rodent malaria parasite *Plasmodium berghei* and an antituberculosis agent (Ang et al., 2000; Higa et al.,



Manzamine A. (From Kasanah et al., *Tetrahedron Lett.*, 44:1291–1293, 2003. With permission.)

2001). Its potent biological activities and its unusual chemical structure led researchers to synthesize and study this compound (Magnier, 1998; Winkler, 1998; Coldham, 2002; Herdemann, 2002; Humphrey, 2002). A synthetic analogue of manzamine, Mana-Hox, was shown by Tu and coworkers (2004) to be cytotoxic against tumor cells with an IC₅₀ ranging from 1 to 5 μ M. Apoptosis was induced as a result of chromosome missaggregation.

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Marine products

, see also Bryostatin, Glucosamine/Chondroitin sulfate, Halichondrin B, Manoalide, and Manzamine A Over the past several decades, scientists have identified a core group of bioactive marine products with potential therapeutic properties. In a review by Faulkner (2000), a number of pharmacologically active products were reviewed, including bryostatins, curacin A, debromohymenialdisine, didemnin, discodermolide, dolastatin, ecteinascidin, eleutherobin, halichondrin B manoalides, pseudopterosins, topsetins, scytonemin, and debromohymenialdisine. One of the limitations is the lack of availability of some of these compounds, although chemical synthesis of manzamine analogues has provided an alternative source (Tu et al., 2004). In addition, aquaculture of marine invertebrates provides an alternative technology for their production, as well as tissue culture of invertebrate cells.

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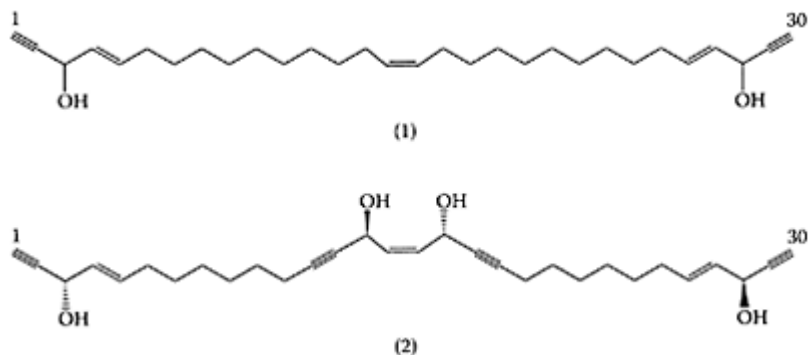
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Marine sponges

see also Manzamine A Marine sponges found in Korean waters included genus *Petrosia*, which contains a number of polyacetylenes that are cytotoxic against several human tumor-cell lines. Kim et al. (1998) first isolated four new polyacetylenes from marine sponge, *Petrosia* sp., with cytotoxicity toward human tumor-cell lines. Several structures were identified, including duryne (1) and petrosynol (2). Kim and coworkers (2002) later showed these polyacetylenes inhibited DNA replication and predominantly inhibited the initiation stage of DNA replication.

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Structures of duryne (1) and petrosynol (2). (From Kim et al., *Tetrahedron*, 54:3151–3158, 1998. With permission.)

Meadowfoam (*Limnanthes alba*)

Meadowfoam is an emerging specialty oilseed crop grown in the Northwestern United States. Its seeds contain 28 percent oil (on a dry basis) and are rich in C20 and C22 monounsaturated fatty acids (Holser, 2003). The low skin irritability and high stability of meadowfoam oil makes it suitable for use in cosmetic formulations and as lubricants (Burg and Kleiman, 1991; Emken et al., 1991; Ricks, 1991).

As mentioned earlier, meadowfoam pressed seed oil is extremely stable, although refining reduces its oxidative stability. Isbell et al. (1999) reported that meadowfoam oil enhanced the oxidative stability of other vegetable oils, suggesting the presence of antioxidants in this oil. Meadowfoam is rich in glucosinolates, such as glucolimnanthin, but these have little or no antioxidant activity (Plumb et al., 1996). However, Abbott and coworkers (2002) isolated a number of compounds in meadowfoam oil capable of forming 1,3-di(3-methoxybenzyl)thiourea (3MBTU) or its oxidation products. Several degradation products from glucolimnanthin, 3-methoxybenzyl isothiocyanate, and 3-methoxybenzylamine, were identified as both capable of forming 3MBTU. The latter compound proved to be an effective antioxidant by enhancing the oxidative stability of a number of vegetable oils, including rapeseed, jojoba, and sunflower oils at a level of 0.1 percent. The potential nutraceutical benefits from meadowfoam remain to be established,

although the presence of glucosinolates and their corresponding isothiocyanates are known for their health benefits.

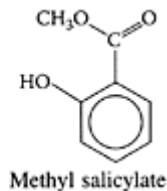
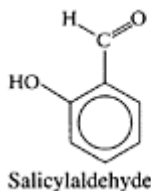
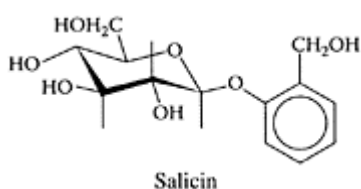
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Meadowsweet (*Filipendula ulmaria*)

Meadowsweet, a fragrant herb with small, white flowers that appear like umbels at the top of the stalks, blossoms from June to September. It can be found by river banks and in moist meadows. Historically, meadowsweet was used by herbalists for a wide variety of conditions, such as rheumatic complaints, muscle aches, headaches, colds and flu, digestive upsets, menstrual cramps, congestive heart failure, and as a diuretic agent (Gruenwald et al., 1998; Duke, 2000; Skidmore-Rose, 2001).

The primary constituents in meadowsweet are salicylates, including salicin, salicylaldehyde, and methyl salicylate, which are thought to contribute to its antiplatelet activity. In the digestive



Adapted from Brenna, et al., *J. Agric. Food Chem.*, 52:7747–7751, 2004.

tract these compounds are oxidized to salicylic acid, a substance closely related to aspirin (acetyl-salicylic acid), which may give it a mild anti-inflammatory effect (Bernaurov and Denisenko, 1980) and an ability to reduce fevers during a cold or flu. The complimentary inhibitory activities reported by Halkes et al. (1997) are in line with its therapeutic value in inflammatory diseases.

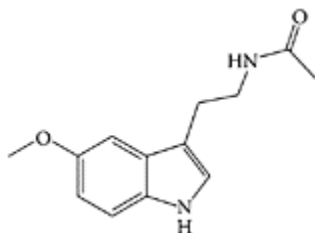
Other constituents include flavonoids, mainly in the flowers, which exhibit considerable antioxidant and antimicrobial activity (Rauha et al., 2000), phenol glycosides (Horhammer, 1956; Thieme, 1966), tannins (Novikova, 1969), and essential oil. Kudriashov et al. (1990) reported that the flowers also contained a heparin-like anticoagulant factor, which demonstrated fibrinolytic properties *in vivo* activities (Peresun'ko, 1993).

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Melatonin

Melatonin (N-acetyl-5-methoxytryptamine), the main hormone of the pineal gland, is synthesized from the amino acid tryptophan via serotonin. It decreases with age so that supplementation may be beneficial in



Melatonin. (Adapted from Sun et al., *Bioorg. Med. Chem. Lett.*, 20:5157–5160, 2004.)

delaying age-related conditions. In addition to being a potent scavenger of free radicals (Reiter, 1997), melatonin may modulate the immune system and the growth of cancer cells (Maestroni et al., 1986; Blask et al., 1992). Hattori and coworkers (1995) identified melatonin in edible plants that would increase the amount of circulating levels in vertebrates. Medicinal plants, such as feverfew, was shown to be a good source of melatonin (Murch et al., 1997). A significant source of melatonin was found by Zielinski and coworkers (2001) in germinated legumes, which increased fourfold to eightfold in soybean, vetch, and lentil seeds, respectively, compared to the raw seeds. Of the three legumes examined, germinated vetch and soybean were almost twice as high in melatonin compared to germinated lentil seeds.

Melatonin was also found to prevent gastric ulceration in pigs (Ayles et al., 1996; Khan et al., 1990) and reduce the severity of colitis in mice (Pentney and Bubenik, 1995). Teplitzky et al. (2001) showed that a combination of melatonin and 9-*cis*-retinoic acid significantly inhibited tumor development in an *N*-nitroso-*N*-methylurea (NMU)-induced rat mammarytumor model. Stavinsky et al. (2005) showed melatonin enhanced *in vivo* and *in vitro* plasmalemmal fusion (PEG-fusion) of severed rat sciatic axons. This may prove beneficial in repairing crush-type injuries to sciatic nerves and spinal chords in accidents involving humans.

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Mengkudu

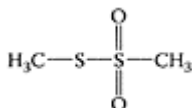
Mengkudu (*Morinda citrifolia* L.), or Indian mulberry, is found in tropical Asia or Polynesia. Its roots are reported to be good sources of anthroquinones (Thomson, 1971; Zenk et al., 1975). Studies by Zin and coworkers (2002) showed that a methanol extract of Mengkudu root had equivalent antioxidant activity to that of α -tocopherol and butylated hydroxyquinone (BHT). Some of the medicinal properties associated with this tree, such as the relief of rheumatic and other pains, may be due to its antioxidant capacity.

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S-Methylmethane thiosulfonate

S-Methylmethane thiosulfonate is found in cruciferous vegetables such as cabbage, onions, and cauliflower. It is formed from its precursor, S-methyl-L-cysteine sulfoxide. Coadministration of S-methylmethane thiosulfonate, isolated from cauliflower, with the nonsteroidal, antiinflammatory drug sulindac, was shown by Reddy et al. (1999) to inhibit chemically induced colon cancer in weanling male F344



S-Methylmethane thiosulfonate. (From Reddy et al., *Carcinogenesis*, 20:1645–1648, 1999. With permission.)

rats. A combination of 40 ppm S-methylmethane thiosulfonate and 160 ppm sulindac resulted in a far more significant ($p<0.05$) inhibition of noninvasive adenomas (59 percent) during the promotion/progression stages, as well the multiplicity of noninvasive (71 percent inhibition), invasive (39 percent inhibition), and total colon adenomas (48 percent) compared to administration with either S-methylmethane thiosulfonate or sulindac, separately. This confirms earlier work by Kawamori and coworkers (1995) who showed that a diet containing S-methylmethane thiosulfonate inhibited azoxymethane-induced colon carcinogenesis in male F344 rats. The mechanism of action by S-methylmethane thiosulfonate was attributed to its ability to decrease mucosal ornithine decarboxylase, a rate-limiting enzyme in polyamine biosynthesis and cell proliferation.

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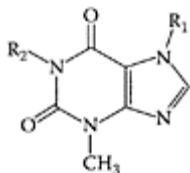
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Methylxanthines

see also Caffeine Methylxanthines include any of the methylated derivatives of xanthine, such as caffeine, theobromine, and theophylline, and their derivatives. Caffeine is found in coffee, tea, cola nuts, mate, and guarana. Its major effects include stimulation of the

central nervous system, cardiac muscle, respiratory system, and diuretic delays disease. Theophylline, a methylxanthine found in tea, is a cardiac stimulant, smooth-muscle relaxant, diuretic, and vasodilator. Theobromine, the main methylxanthine in cocoa beans (1.5–3 percent), cola nuts, and tea, is a diuretic agent, smooth-muscle relaxant, cardiac stimulant, and vasodilator (Shively and Tarka, 1984; Spiller, 1984; Youd et al., 1999; Vajner et al., 2002; Nawrot et al., 2003).

In humans, caffeine acts on the brain and skeletal muscles, while theophylline targets heart, bronchia, and kidneys. Recent interest in these alkaloids is centered on their potential reproductive toxicities.



CF: $R_1 = -CH_3$

$R_2 = -CH_3$

TB: $R_1 = -CH_3$

$R_2 = -H$

TP: $R_1 = -H$

$R_2 = -CH_3$

Methylxanthine structures: CF, caffeine; TB, theobromine; and TP, theophylline. (From Lopez-Martinez et al., *Analytica Chimica Acta*, 493:83–94, 2003. With permission.)

Caffeine and theobromine are known to cross the placental and blood-brain barriers, potentially capable of inducing fetal malformation by affecting expression of genes vital in development. The developing fetus may not have developed enzymes for detoxification of these methylxanthine alkaloids via demethylation. Evidence in favor of the toxicity of these compounds in experimental animals was presented by Eteng and coworkers (1997), who cautioned against the use of caffeine and theobromine pending further and more elaborate investigations. On the other hand, Slattery et al. (1999) showed that among men, low levels of coffee intake were associated with increased risk of colon cancer relative to nonconsumers of coffee, while at high levels of coffee consumption, caffeine and theobromine both inhibited the doxorubicin efflux from tumor cells, increased the doxorubicin concentration in a tumor, and thus enhanced the antitumor effect of doxorubicin, suggesting these xanthine derivatives may be useful for biochemical modulators.

Methylxanthines are used clinically as bronchodilators (Henderson-Smart and Steer, 2000, 2001). The precise mechanism whereby methylxanthines exert their beneficial effect in apnea, a problem of ventilatory control in the premature infant, defined as cessation of inspiratory gas flow for 20 sec or less if accompanied by bradycardia, cyanosis, or pallor, is not known. Proposed mechanisms include increased respiratory drive secondary to increased carbon-dioxide sensitivity and increased oxygen consumption. Other mechanisms postulated include adenosine antagonism, enhanced diaphragmatic contractility, and increased cyclic 3',5'-cyclic AMP (Henderson-Smart and Steer, 2000, 2001). Johnson and coworkers (2003) demonstrated that the discrimination

in the binding affinity of the methylxanthines, theophylline, theobromine, and caffeine with RNA molecule shows that strong, RNA-binding drugs, such as theophylline, can selectively be delivered to RNA targets of microbial pathogens having the mechanism of RNA catalysis. The controversies surrounding xanthine therapy for apnea in premature infants was reviewed by Millar and Schmidt (2003). They reported that an international trial was under way to examine the long-term efficacy and safety of methylxanthine therapy for very low-birth-weight babies.

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Milk proteins

see also Casein and Whey Proteins Lactoglobulin Milk proteins, caseins, and whey proteins serve as important nutritional sources in the diet. The susceptibility of caseins to

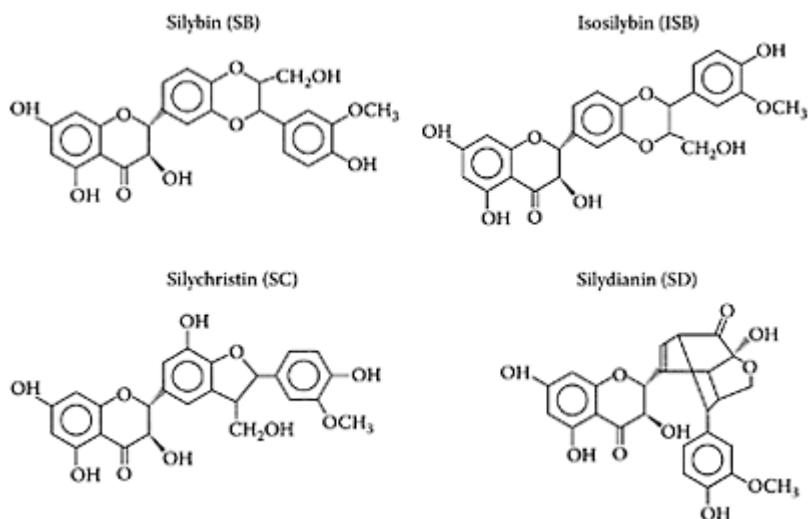
proteolysis, however, produces physiologically functional peptides, immunostimulating peptides (Parker et al., 1984), and angiotensin 1-converting enzyme inhibitors (ACEI). There have been many antihypertensive peptides produced by enzymic digestion of bovine and human caseins (Yamamoto and Takano, 1999). Those high in ACEI activity tend to be fairly short peptides with proline in the C-terminus. There is limited work on ACEI peptides from whey proteins due to the rigid structure and resistance to digestive enzymes of the major component, β -lactoglobulin. Nevertheless the enzymatic production of ACEI peptides from whey proteins was recently reported (Mullaly and coworkers, 1996, 1997). ACEI peptides were also found to be present in sour milk produced by starter cultures, *Lactobacillus helveticus* and *Saccharomyces cerevisiae* (Nakamura et al., 1995a, b). Balansky and coworkers (1999) showed that freeze-dried milk fermented by a *Lactobacillus bulgaricus* strain inhibited 1,2-dimethylhydrazine (DMH)-induced carcinogenesis. The effect varied with the particular *Lactobacillus bulgaricus* strain studied. For example, strain LBB.B144, whose product, FFM.B144, inhibited the intestinal carcinogenesis induced by DMH, as well as decreased tumor incidence and multiplicity in male and female rats in the large bowel, caecum, and duodenum. This contrasted with strain LBB.B5, whose product, FFM.B5, selectively inhibited DMH-induced carcinogenesis of the large bowel only. Both products significantly inhibited (26–33 percent) the induction of earduct tumors in rats, while only FFM.B144 inhibited tracheal carcinogenesis induced by diethylnitrosamine (DEN) in Syrian hamsters. These results pointed to the potential of some fermented-milk products in the chemoprevention of cancer.

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Milk thistle

Milk thistle, a medicinal herb native to the Mediterranean region, has been used for centuries as a remedy for liver ailments. The active ingredient in milk thistle is silymarin, a bioflavonoid mixture composed mainly of silybin with silydianin and silychristin (Scheme M.39). They are all liver protectants (antihepatotoxic agents), as studies showed they protect the liver from a wide range of toxins, including the deadly *Amanita phalloides* mushroom, or Death Cap mushroom. Silymarin has also been found to protect the liver from dangerous solvents, such as carbon tetrachloride and ethanol. Studies in Germany showed considerable improvement in patients suffering from chronic hepatitis after three months of treatment with silymarin. Daily doses of up to 420 mg of silymarin were shown to improve almost 50 percent of patients suffering



SCHEME M.39 Structures of the main silymarin components (From Kvasnicka et al., *J. Chromatogr. A.*, 990:239–245, 2003. With permission.)

from cirrhosis of the liver. Silymarin appears to accelerate regeneration and production of liver cells. Because silymarin is insoluble in water, it is available in capsule form. In the United States, it is marketed as a food supplement in 200–250 mg capsules containing up to 80 percent silymarin. The beneficial effects are attributed to its antioxidant properties, as silymarin was reported to prevent lipid peroxidation (Velussi et al., 1997; Lahiri-Chatterjee et al., 1999), inhibit LDL oxidation (Skottova et al., 1999), and scavenge free radicals (Dehmlow et al., 1996a, b).

A systematic review and meta-analysis of milk thistle by Jacobs and coworkers (2002) concluded that milk thistle was safe and welltolerated. However, the authors felt that the data were too limited to exclude a substantial benefit or harm from milk thistle on mortality or to recommend its efficacy for treating liver disease. Nevertheless, recent work by Gurley and coworkers (2004) using human subjects reported that botanical supplements, such as milk thistle, posed minimal risk for CYP-mediated herb-drug interactions in humans.

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Mistletoe (*Viscum album* L.)

Mistletoe is a half-parasitic plant that grows on deciduous trees all over the world (Barney et al., 1998). A traditionally valued medicinal plant, it has been used against high blood pressure, arthritis, cardiovascular illness, epilepsy, and as a narcotic. Extracts from mistletoe have been used in the treatment of cancers for decades. The anticancer activities are ascribed to the plant's viscotoxins (Konopa et al., 1980; Jung et al., 1990), lectins (Jung et al., 1990; Bussing, 1996), alkaloids (Khwaja et al., 1986), and polysaccharides (Jordan and Wagner, 1986), which vary, depending on the host tree, the subspecies of mistletoe, and the parts used and the time of harvest (Jaggy et al., 1995; Barberaki and Kintzios, 2002). Numerous preclinical and *in vitro* studies showed the mistletoe extracts

standardized in terms of their lectin content have highly potent cytotoxic and immunostimulating effects, predominantly on the cellular immune system (Schink, 1997; Beuth, 1997; Elsaesser-Beile et al., 1998; Stauder, 2002). The immunostimulating effect is correlated with the apoptosis of immunologically active cells at low concentrations. Cytotoxic effects on tumor cells are likewise, but at high level, necrotic cell death predominates. Due to these properties, mistletoe extracts exhibited antitumoral activities in different animal models (Mengs et al., 2002). Pryme et al. (2002) showed that the growth of murine non-Hodgkin lymphoma (NHL) tumor was reduced by incorporating mistletoe lectin into the diet. The degree of lymphocyte infiltration was increased in tumors from mistletoe-lectin-fed mice, and this was accompanied by a high incidence of apoptotic bodies. Visual observation of NHL tumors from individual mice fed mistletoe-lectin-rich diets showed a reduction in tumor weight followed by poorly developed blood supply in contrast to control-fed mice, which suggested an antiangiogenic response. Translation of these effects into a clinical response continues to pose a problem. While a number of clinical studies found improvement in the quality of life, data on the efficacy of mistletoe to prolong survival are conflicting and of variable quality (Mansky, 2002; Stauder and Kreuser, 2002).

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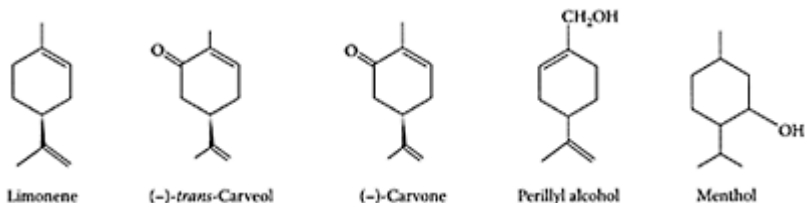
Monoterpenes

see also Geraniol, Limonene, Menthol, Perillyl alcohol, and Perrialddehyde

Monoterpenes are found in essential oils of citrus fruits, cherry, mints, and herbs. These 10-carbon isoprenoids are synthesized in plants via the mevalonate pathway but cannot be produced by fungi or mammals. Monoterpenes are largely responsible for the distinctive fragrance of many plants and function as chemoattractants or chemorepellents (McGarvey and Croteau, 1995). Limonene, one of the first monoterpenes produced from mevalonate, acts as precursor for a wide array of oxygenated, monocyclic monoterpenes, including carveol, carvone, menthol, perillyl alcohol, and perillaldehyde.

Some monoterpenes have been shown to have antitumor activity capable of not only preventing the formation and progression of cancer but also to regress malignant tumors (Crowell, 1999). These include d-limonene (Kawamori et al., 1996), carveol (Crowell et al., 1992), menthol (Russin et al., 1989), geraniol (Yu et al., 1995), and perillyl alcohol (Mills et al., 1995). Chan (2001) reviewed the potential medicinal uses of monoterpenoid compounds, as well as assay methods.

The cancer-suppressing activity of monoterpenes during the promotion phase of mammary and liver carcinogenesis is thought to be due to inhibition of tumor-cell proliferation, acceleration of the rate of tumor death, and induction of tumor-cell differentiation (Morse and Stoner, 1993). Antitumor activity by limonene and other monoterpenes appears to be due to the induction of phase I and phase II carcinogenmetabolizing enzymes. Inhibition of protein isoprenylation prevents carcinogenesis, as prenylation of Ras enables it to associate with the plasma membrane, an essential step for its oncogenic activity (Clarke, 1992). Consequently, the antitumor activity of monoterpenes appears to be due to their effect on prenylationindependent mechanisms or prenylation of proteins other than Ras.



Structures of monoterpenes. (Adapted from Chan, *J. Chromatogr. A.*, 936:47–57, 2001; Carter et al., *Phytochemistry*, 64:425–433, 2003; Tasarti et al., *J. Catal.*, 224:484–488, 2004.)

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Mushrooms

see also Oyster mushroom Yang and coworkers (2001) recently examined the nutritional values of a number of commercial mushrooms. Some of these mushrooms were found to have medicinal properties, including antitumor, antiviral, and immunomodulating effects (Wasser and Weis, 1999). Of these mushrooms, shiitake and oyster mushrooms were shown by Yang et al. (2002) to exhibit antioxidant activity as assessed by the formation of TEA-active components and the scavenging of 1,1-diphenyl-2-picrylhydrazyl radicals. Oyster mushrooms exhibited to highest scavenging activity

Kim et al., (2004) recently reported that in addition to anti-angiogenic activity, a butyl alcoholic extract from the orange color mushroom, *Phellinus linteus*, exhibited anti-inflammatory and antinociceptive activities.

References

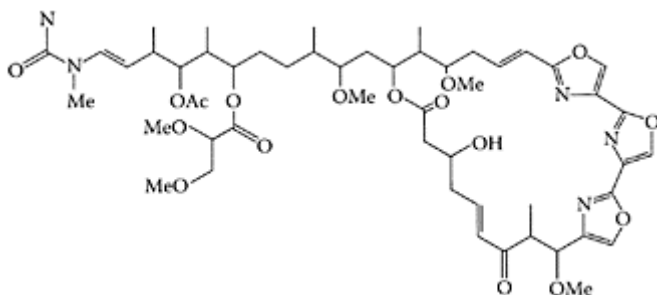
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Mustard

see Yellow mustard

Mycalolide A-C

Mycalolides A-C are cytotoxic macrolides isolated from a sponge of the genus *Mycale*. They are trisoxazole-containing natural products and include ulapualides, kabiramides, halichondramides, and jaspisamides. These natural products display a wide range of biological activities, such as antifungal,



Chemical structure of mycalolide-B. (From Hori et al, *FEBS Lett.*, 322:151–154, 1993. With permission.)

antileukemic, and ichthyotoxic properties. Mycalolide A exhibits potent antifungal activity against a diverse array of pathogenic fungi and cytotoxicity towards B-16 melanoma cells with IC_{50} values of 0.5–1.0 ng/mL (Fusetani et al., 1989). The ability of mycalolide-B to selectively inhibit actin polymerization and actinactivated myosin $Mg(2+)$ -ATPase activity using purified actin and myosin from rabbit skeletal muscle or chicken gizzard was reported by Saito et al. (1994) and Hori et al. (1993), respectively. They suggested that these macrolides can act as actin-depolymerizing agents and may be involved in actin-mediated cell functions, such as muscle contraction, cell motility, and cell division. The relationship between the concentration of total actin and F-actin at different concentrations of mycalolide-B suggests it forms a 1:1 complex with platelet aggregation by interfering with actin polymerization (Sugidachi et al., 1998). Treatment of highly polarized MDCK cells with mycalolide B induced a decrease of transepithelial resistance, which demonstrates the involvement of actin in the paracellular gate, which seals the paracellular space of opposing cells (Takakuwa et al., 2000). Because actin filaments play a critical role in transporting nascent HIV-1 proteins in host cells, Sasaki et al. (2004) examined the effect of mycalolide-B in the process. MycalolideB depolymerized actin, which appeared to prevent HIV- envelope proteins and core proteins from being transported toward the plasma membrane of the host cell. These researchers suggested that chemical modification of mycalolide-B, to reduce its toxicity, might lead to its application in treating AIDS by HIV-1 infection.

A number of novel, stereochemically complex macrolides having a large macrolactone (22- to 44-membered) ring that interact with the actin cytoskeleton have been isolated from different marine sources. Although the details of these interactions are still under investigation, these marine macrolides are important as novel molecular probes to help elucidate the cellular functions of actin (Yeung and Paterson, 1992). These macrolide properties led researchers to synthesize mycalolides as depolymerizing agents (Panek and Liu, 2000).

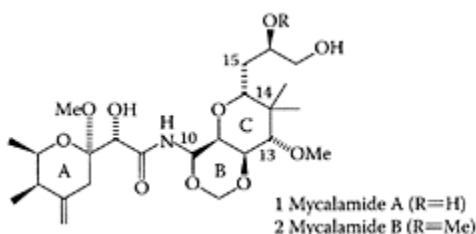
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Mycalamide A, B

Mycalamides A, B, and D, isolated from the New Zealand marine sponge *Mycale* sp., showed close structural similarity to the insect toxin pederin, and exhibited potent cytotoxicity and antitumor activity. All members of the pederin family are rare, difficult to isolate, and comparatively frail.



Structures of mycalamide A and B. (Gardiner et al., *Tetrahedron lett.*, 45:1215–1217, 2004. With permission.)

Mycalamides A and B exhibited potent *in vitro* toxicity and *in vivo* efficacy against murine and human tumor cells. They were reported to inhibit HL-60, HT-29, and A549 human cell tumor lines. Mycalamide A was also active against BV16 melanoma, Lewis lung carcinoma, M5076 ovarian sarcoma, colon 26 carcinoma, and the human MX-1, CX-1, and Burkitt's lymphoma tumor xenografts. Mechanistic studies indicated mycalamides inhibited protein synthesis (Burres and Clement, 1989). Moreover, mycalamide A blocked T-cell activation in mice (Galvin et al., 1993) and induced apoptosis in several cell lines (Hood et al., 2001).

Mycalamides A and B were reported to convert the morphology of ras-transformed NRK-cells to normal morphology by preferentially inhibiting the biosynthesis of p21 protein (Ogawa, 1991). In addition to their biological activity, their unique framework and scarcity from natural sources make these molecules attractive synthetic targets (Jason

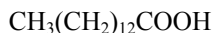
et al., 2003). Trost and coworkers (2004) recently achieved an efficient formal synthesis of (–)-mycalamide A.

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Myristic acid

This short-chain, saturated fatty acid (C14:0) is generally associated with increasing plasma total cholesterol, particularly



LDL cholesterol, in humans (Hays and Khosla, 1997; Hegsted et al., 1965). This was based on diets in which myristic acid accounted for 16 percent of the total dietary energy (Salter et al., 1998) or where cholesterol doses were too low or too high (Nicolosi et al., 1997). Recent research suggests myristic acid is an important cell component, as proteins need to be myristoylated for the transduction pathway, vesicular trafficking, and structural positioning (Boutin, 1997). Maternal milk, considered to be well balanced, contains 9 percent myristic acid, or about 3–4 percent of total energy. Most of it is located in the *sn*-2 position of the triacylglycerol molecule (Jensen et al., 1990). Using golden Syrian hamsters, because of their similarity with human cholesterol metabolism, Loison and coworkers (2002) tested the hypothesis that myristic-acid-containing diets ranging from 0.5–2.4 percent of the total dietary energy had no detrimental effect on

plasma cholesterol. In fact, these researchers, for the first time, found that myristic acid actually increased HDL-cholesterol (HDL-C) via regulation of the hepatic expression of the scavenger receptor B1 (SR-B1). Because of the atheroprotective role of HDL-C, it appears that myristic acid exerted a beneficial effect under these conditions.

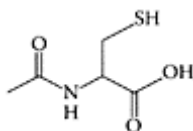
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N

***N*-Acetyl-L-cysteine (NAC)**

N-Acetyl-L-cysteine (NAC), a powerful antioxidant and immune enhancer, is the acylated form of the amino acid cysteine found naturally in foods. NAC is a precursor of glutathione, which functions as a detoxicant and antioxidant in the body



N-Acetyl cysteine (NAC). (Adapted from Coleman et al., *Environ. Toxicol. Pharmacol.* 17:143–148, 2004.)

(Aruoma et al., 1989; De Flora et al., 1995). NAC supplements were reported to improve symptoms, as well as prevent recurrences of chronic bronchitis in patients (Grandjean et al., 2000). A short-term study of patients with adenomatous colonic polyps found NAC significantly decreased the proliferative index (PI) (Estensen et al., 1999). Several case reports with Unverricht-Lundborg disease, an inherited degenerative disorder, was dramatically improved by supplementation with NAC (Kurd et al., 1996; Selwa, 1999). NAC is used as a possible treatment for HIV because *in vitro* studies showed that glutathione-deficient cells are particularly sensitive to inflammatory cytokines, such as tumor necrosis alpha (TNF) (Staal et al., 1992). Using NAC therapy to increase intracellular glutathione levels should prevent stimulation by TNF of nuclear transcription factor kB (NF-κB) in HIV-infected cells, virus transcription, and replication. Certain medications, however, may interact with NAC and should be avoided.

The isomers of NAC, LNAC, and DNAC were recently found by Neal and coworkers (2003) to be effective antioxidants, protecting mice lung from increased malondialdehyde levels and mice liver from increased 8-hydroxy-deoxyguanosine, following 18 Gy whole-body radiation. These results were consistent with the radioprotection and repair processes associated with NAC. Serrano-Mollar et al. (2003) found NAC reduced primary inflammatory events, which prevented cellular damage and pulmonary-fibrosis development in bleomycininduced lung damage in rats.

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Nacystelyn

Nacystelin (NAL), a newly developed lysine salt of *N*-acetyl-L-cysteine (NAC), has been shown to have mucolytic and antioxidant properties. Antonicelli and coworkers (2002) showed NAL had therapeutic potential in inflammatory-lung diseases by its ability to inhibit cytokine release.

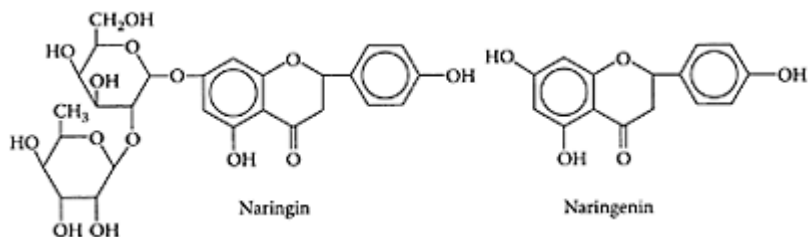
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Naringin and Naringenin

Naringin (4',5,7-trihydroxyflavonone-7-rhamnoglucoside), the major flavonone glycoside in grapefruit, was shown to have antiulcer, as well as superoxide, scavenging and antioxidant properties (Kroyer, 1986; Chen et al., 1990). When digested, naringin is hydrolyzed by the intestinal bacteria to its absorbable aglycone metabolite, naringenin (4',5,7-trihydroxyflavonone) (Ameer et al., 1996). The properties associated with naringin are probably reflected by similar properties observed for naringenin (Parmar, 1983; Kroyer, 1986). In addition, naringenin was also found to have vasodilatory, as well as anticancer, properties (Rojas et al., 1996; So et al., 1996). The health benefits reported for naringin are probably due to the formation of its hydrolyzed metabolite, naringenin. For example, recent studies by Singh and Chopra (2004) attributed the radical-scavenging and antioxidant properties of naringin to its renoprotective effect against reactive-oxygen species, which play a major role in the pathogenesis of renal ischemia, a common cause of acute renal failure. Because of the absence of acute or chronic toxicity, they suggested naringin had clinical application in the prevention of ischemia-reperfusion. However, the antioxidant properties of naringin were also shown by Kanno and coworkers (2004) to interfere with the cytotoxicity and apoptosis-inducing oxidative stress exerted by the antimetabolite chemotherapeutic drug, cytosine arabinoside, in the treatment of acute leukemia.

The ability of naringin to inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis, pointed to its potential as a cholesterol-lowering and antiatherogenic agent (Bok et al., 2000; Shin et al., 1999). Using the rabbit as the animal model, Jeon et al. (2004) recently compared the hypocholesterolemic action of naringin and lovastatin, a drug used for lowering cholesterol. Male rabbits were maintained on a 0.5 percent high-cholesterol diet with either 0.05 percent naringin or 0.03 percent lovastatin



Structure of naringin and naringenin. (From Kanaze et al., *J. Chromatogr. B.*, 801:363–367, 2004.)

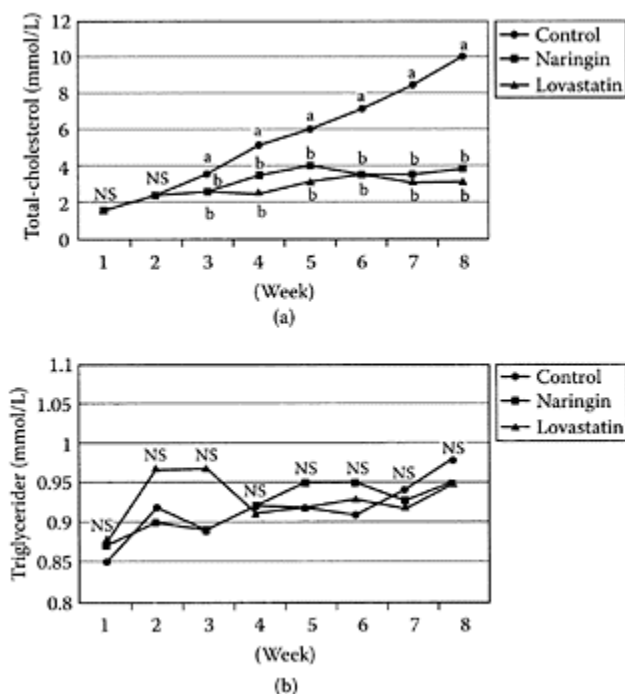


FIGURE N.67 Effects of naringin and lovastatin supplements for eight weeks on changes of plasma total cholesterol (a) and triglyceride (b) concentrations in high-cholesterol-fed rabbits. Values are mean \pm SEM, n=5. ^{ab}Values not sharing a common letter are significantly different among groups at $p<0.05$. ^{NS}Values are not significantly different among groups at $p<0.05$. (Jeon et al., *Clin. Nutr.*, 23:1025–1035, 2004. With permission.)

over eight weeks. While the plasma triacylglycerols were unaffected by any of the treatments, there was a significant ($p<0.05$) decrease in plasma total cholesterol, LDL cholesterol, and atherogenic index in animals treated with naringin or lovastatin. Naringin appeared to be as effective as lovastatin in lowering cholesterol, as shown in Figure N.67, for plasma total-cholesterol levels. Plasma HDL cholesterol was significantly higher in the naringin-fed group only. The cholesterol-lowering action of naringin was attributed to being mediated by a combination of acyl-CoA: cholesterol acyltransferase (ACAT) inhibition and increased sterol excretion.

The hypocholesterolemic properties of naringenin and several derivatives have also been demonstrated by Lee et al. (2003a). Two classes of naringenin derivatives, naringenin 7-*O*-oleic acid and naringenin 7-*O*-cetyl ether, both significantly reduced the formation of atherosclerotic lesions in rabbits fed a high-cholesterol (1 percent) diet, as shown in Figure N.68. However, the antiatherogenic effects could not be attributed to plasma-lipid levels so that another mechanism must be involved. Using rats, Lee and coworkers (2003b) showed naringenin 7-*O*-cetyl ether inhibited HMG-CoA reductase, as well as modulated plasma and hepatic lipids, when fed a high-cholesterol diet. Bernini and coworkers (2003) showed that naringenin lactone, formed from naringenin by the Baeyer-Villiger reaction, induced apoptosis in an E2 human lymphoma-cell line, normally resistant to apoptosis.

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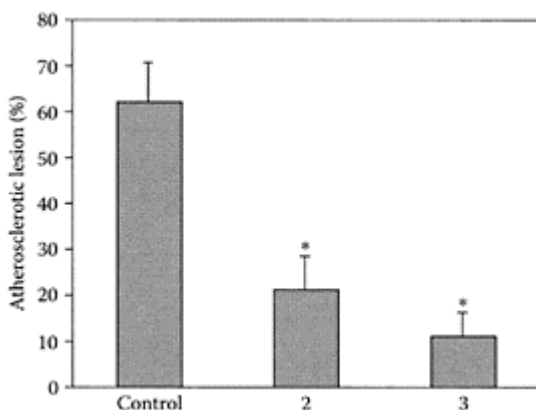


FIGURE N.68 Effects of naringenin 7-*O*-oleic ester (2) and naringenin 7-*O*-cetyl ether (3) on the aortic fatty streak formations in rabbit model fed a high-cholesterol diet for eight weeks. A graph of atherosclerotic lesion size expressed as a percentage of the oil red-O positive area/measured internal surface in each group. Bars represent standard deviations. * is significantly different ($p < 0.01$) from control group. (Lee et al., *Bioorg. Med. Chem. Lett.*,

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permission.)

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Nettle (*Urtica dioica* L.)

Nettles (*Urtica dioica* L.) are recognized for the stinging hairs on the leaves and stems, which release formic acid and histamine on the skin when touched. Nevertheless, many of these constituents (formic acid, acetylcholine, 5-hydroxytryptamine, and histamine) appear to have antiarthritic and antirheumatic properties. One of the best-known uses of nettles is for the treatment of gout and other rheumatic conditions by mobilizing uric acid from the joints and eliminating it through the kidney.

Aqueous extracts from nettles are used to treat a variety of ailments. In Morocco, for example, it is used as a hypotensive and antidiabetic agent (Bnouham et al., 2002). Significant antihyperglycemic effects observed with aqueous extracts from *Urtica dioica* were attributed, in part, to a reduction in intestinal glucose absorption (Bnouham et al., 2003). Farzami and coworkers (2003) also examined the blood-glucose-lowering effect of nettles and identified an active fraction, F₁, in extracts from nettles that enhanced insulin secretion from Islets of Langerhans.

The efficacy of nettle extracts as adjuvants in the treatment of rheumatism was attributed to their ability to inhibit expression of cytokines, as well as eicosanoid formation, in stimulated peripheral blood cells (Obetreis et al., 1996; Teucher et al., 1996). Subsequent work by Reihemann and coworkers (1999) showed that part of the anti-inflammatory action by nettle extracts involved inhibition of NF- κ B activation. NF- κ B, a family of transcription factors, is involved in the inducible expression of many genes involved in inflammatory responses (Baeuerle and Henkel, 1994; Barnes and Karin, 1997). These results are consistent with traditional antirheumatic drugs, which also exert part of their anti-inflammatory effects by interfering with the NF- κ B pathway (Auphan et al., 1995; Sheinman et al., 1995; Wahl et al., 1998). A recent study by Gulcin et al. (2004) showed that a water extract from nettles exhibited antioxidant, antimicrobial, antiulcer, and analgesic properties.

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Niacin and Nicotinamide

Niacin or nicotinic acid, β -pyridine carboxylic acid, is a water-soluble B vitamin that is readily converted into its physiologically active form, nicotinamide. Nicotinic acid was first reported a half a century ago by Altschul et al. (1955) to lower serum cholesterol in man. A subsequent study by Canner et al. (1986) used pharmacological doses of nicotinic acid as a hypolipidemic agent in the Coronary Drug Project to improve long-term survival after myocardial infarction. Niacin lowered plasma triglycerides and total and LDL cholesterol, while increasing HDL levels. The mechanism of action appeared to involve inhibition of peripheral lipolysis and VLDL synthesis and shunt of apolipoprotein B degradation, together with decreased apo A-I removal (Grundy et al., 1981; Jin et al., 1989). The reduced cellular cholesterol content and enhanced HDL-mediated cholesterol efflux appeared to result from the effects of niacin on the transcription of several key transporters and receptors involved in reverse cholesterol transport (Rubic et al., 2004). Signaling pathways transmitting niacin effects suggested a role for niacin-induced prostaglandin D₂ formation and activation of peroxisome proliferator-activated receptor gamma (PPAR γ) in expression of the combined adhesion and scavenger receptor CD36.

A combination of statins, cholesterol-lowering drugs, and niacin were reported to produce clinical and angiographic benefits in patients suffering from coronary heart disease in an HDL-Atherosclerosis Treatment Study (HATS) (Brown et al., 2001). A three-year study by Zhao et al. (2004) on 160 patients with coronary heart disease found that a mean daily dose of simvastatin-niacin (13 mg and 4 mg, respectively) halted the progression of angiographic atherosclerosis. In addition, patients with low HDL had a reduction of 60 percent in the major clinical events associated with the disease compared to the placebos. A combination of simvastatin and niacin proved to be an effective and safe treatment that was well-tolerated by patients with or without diabetes mellitus. The therapeutic potential of niacin/statin combinations was also demonstrated by Bays and

coworkers (2003) in a 16-week treatment of 315 patients (with elevated LDL cholesterol and low HDL cholesterol). A combination of extended-release niacin (niacin ER) and lovastatin proved far more effective in improving lipid profiles than either simvastatin or atorvastatin, as summarized in Table N.48.

In addition to the cholesterol-lowering effects of nicotinic acid, the cytoprotective and antiviral properties of nicotinamide is also receiving increasing attention. Maiese and Chong (2003) suggested nicotinamide may slow down degenerative diseases associated with the central nervous system. Another study implicated nicotinamide in the prevention of AIDS (Murray, 1999). Gaudineau and Auclair (2004) recently reported inhibition of human P450 enzymes by nicotinic acid and nicotinamide. The ability to inhibit P450 enzymes raises serious questions regarding the consumption of large, pharmacologically active doses of this vitamin in light of potential drug interactions when using multidrug therapies. Several recent reviews on the lipid-lowering properties of niacin are recommended (Ganji et al., 2003; Rosenson, 2003).

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TABLE N.48
Percent Change from Baseline Following
Niacin/Lovastatin, Atorvastatin, and
Simvastatin Treatments

	Niacin ER/Lovastatin		Atorvastatin	Simvastatin
Week 8	1,000/40 mg	1,000/40 mg	10 mg	10 mg
LDL cholesterol	–38% [†]	–40% [†]	–38% [†]	–28%
HDL cholesterol	+20% ^{†‡}	+20% ^{†‡}	+3%	+7% [‡]
Triglycerides	–30% ^{†‡}	–35% ^{†‡}	–20%	–18%
Lipoprotein(a)	–16% ^{†‡}	–14% [‡]	+8%	0% [‡]
Week 12*	1,000/40 mg	1,500/40 mg	20 mg	20 mg
LDL cholesterol	–42% [†]	–42% [†]	–45% [†]	–35%
HDL cholesterol	+19% ^{†‡}	+24% ^{†‡}	+4%	+8% [‡]
Triglycerides	–36% ^{†‡}	–42% ^{†‡}	–30% [†]	–15%

Lipoprotein(a)	−20% ^{†‡}	−17% ^{†‡}	+2%	−1%
Week 16*	1,000/40 mg	2,000/40 mg	40 mg	40 mg
LDL cholesterol	−39%	−42%	−49% ^{†§}	−39%
HDL cholesterol	+17% ^{†‡}	+32% ^{†‡}	+6%	+7%
Triglycerides	−29% [†]	−49% [†]	−31% [†]	−19%
Lipoprotein(a)	−19% ^{†‡}	−21% ^{†‡}	0%	−2%

Note: LDL and HDL cholesterol are expressed as mean values, and triglycerides and Lp(a) are expressed as median values.

* Dosage is milligrams per day.

[†] $p \leq 0.05$ versus Simvastatin.

[‡] $p \leq 0.05$ versus atorvastatin.

[§] $p \leq 0.05$ versus niacin ER/lovastatin 1,000/40 and 2,000/40 mg.

Source: From Bays et al., *Am. J. Cardiol.*, 91:667–672, 2003. With permission.

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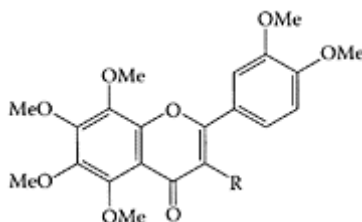
Zhao, X.-Q., Morse, J.S., Dowdy, A.A., Heise, N., DeAngelis, D., Frohlich, J., Chait, A., Albers, J.J., and Brown, B.G., Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low-high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study), *Am. J. Cardiol.*, 93:307–312, 2004.

Nicotinic Acid

see Niacin

Nobiletin

Nobiletin (5,6,7,8,3',4'-hexa-methoxyflavone) is a polymethoxyflavonoid present in citrus fruit, including tangerines, sweet orange peel (*Citrus sinensis*), and in bitter orange (*Citrus aurantium*) (Horowitz and Gentili, 1977). Kohno et al. (2001) reported that nobiletin suppressed the formation of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) in rats. This was evident by the significant reduction in the frequency of



Nobiletin. (From Iwase et al., *Cancer Lett.*, 163:7– 9, 2001. With permission.)

ACF of 55 percent and 50 percent when nobiletin was fed over a five-week period at doses of 0.01 percent and 0.05 percent, respectively. The anti-inflammatory action of nobiletin was demonstrated by Ishiwa et al. (2000), who showed it suppressed the production of promatrix metalloproteinase (proMMP)-9/progelatinase B in rabbit synovial fibroblasts. High levels of the latter are found in the synovial tissues and fluid of patients with rheumatoid arthritis (Tetlow et al., 1993). Lin et al. (2003) further explored the anti-inflammatory properties of nobiletin and showed it interfered with the production of PGE₂ (Figure N.69). In contrast to interleukin-1 α (IL-1 α), which augmented PGE₂ production tenfold (treatment 2), nobiletin suppressed the IL-1 α mediated production of PGE₂ in a dose-dependent manner (4–64 mM; treatments 3–7). For example, a 65 percent reduction of IL-1 α -induced PGE₂ production was evident by the presence of 4 mM nobiletin (treatment 3). Nobiletin interfered with PGE₂ production in human synovial fibroblasts by

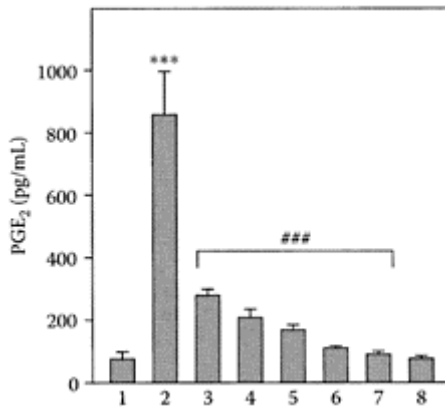


FIGURE N.69 Suppression of PGE₂ production by nobiletin in human synovial fibroblasts. Confluent synovial cells, at passage 10, were treated in 24 multiwell plates with recombinant human interleukin-1 α (rhIL-1 α) (1 ng/mL) and nobiletin in 1.0 mL of DMEM/0.2 percent LAH for 24 h. The amount of PGE₂ released in the culture medium was determined by enzyme immunoassay. Treatments: 1, control; 2, rhIL-1 α ; 3–7, rhIL-1 α plus nobiletin (4, 8, 16, 32, and 64 mM, respectively); and 8, nobiletin (64 mM). Data are the means of \pm SD for quadruplicate wells. Key: (***) and (###), significantly different from the control ($p < 0.001$) and the rhIL-1 α -treated cells ($p < 0.001$), respectively, (Lin et al., *Biochem. Pharmacol.*, 65:2065–2071, 2003. With permission.)

down regulating of the COX-2 gene, while decreasing the expression of IL-1 α , IL-1 β , TNF- α , and IL-6 mRNAs in mouse macrophages. Based on these results, nobiletin appeared to have considerable potential as an immunomodulatory and anti-inflammatory drug.

The possible role of nobiletin in the prevention of atherosclerosis was reported by Whitman et al. (2005) because of its ability to reduce plasma cholesterol levels. Nobiletin inhibited acetylated LDL (acLDL)-mediated accumulation of cholesterol esters in culture murine macrophages by 50–72 percent by an unknown mechanism, as it did not affect SR-A protein expression. In addition to reducing plasma cholesterol, it may also inhibit macrophage foamcell formation.

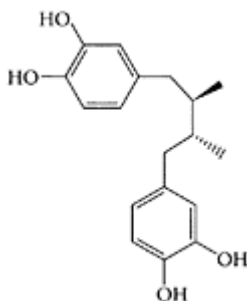
Tanaka and coworkers (2004) proposed nobiletin as a new sunscreen reagent because of its ability to inhibit PGE₂ production by ultraviolet B (UVB) irradiation. Nobiletin suppressed COX-2 expression and decreased the activity of cytosolic phospholipase A (CPLA) in UVB-irradiated human keratinocytes. Its ability to prevent UVB-induced photoinflammation and photoaging of human keratinocytes makes nobiletin a potential sunscreen reagent.

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Nordihydroguaiaretic acid

Nordihydroguaiaretic acid (NDGA) is also known as β , γ -dimethyl- α , delta-bis-(3,4-dihydroxyphenyl)butane; 4,4'-(2,3-dimethyltetramethylene)



Nordihydroguaiaretic acid. (From Lambert et al., *Toxicol.*, 40:1701–1708, 2002.)

dipyrrocatechol. It is a constituent of the creosote bush *Larrea divaricata* and well known to be a selective inhibitor of lipoxygenases.

NDGA can also inhibit platelet-derived growth factor and the protein kinase C intracellular signaling family, which both play an important role in proliferation and survival of cancers. In fact, NDGA was shown to induce apoptosis in tumor xenografts (McDonald et al., 2001). NDGA is a lignan also found in large amounts (up to 10 percent by dry weight) in the leaves and twigs of *L. tridentata* capable of inducing cystic nephropathy in the rat, with intraperitoneal administration of NDGA being lethal in the mouse ($LD_{50}=75$ mg/kg) (Lambert et al., 2002). It can also block protein transport from the endoplasmic reticulum (ER) to the Golgi complex and induce the redistribution of Golgi proteins into the ER (Fujiwara et al., 2003). Ono and coworkers (2002) showed NDGA inhibited fA β formation from A β and breaks down fA β *in vitro*, which suggests it could be a key molecule for the development of therapeutics for Alzheimer's disease. More recently Nakamura et al. (2003) reported NDGA protected microtubules in NRK cells from depolymerization caused by diverse drugs, suggesting NDGA belonged to a novel family of microtubule-stabilizing drugs. NDGA has been used as an antioxidant in oils and foods. Specific inhibition of peroxidase, catalase, ethyl alcohol dehydrogenase, was shown to occur in the presence of 2×10^{-4} M of the antioxidant. Nonspecific inhibition of ascorbic-acid oxidase, D-amino-acid oxidase, the cyclophorase system, and urease have been reported in the presence of 2×10^{-4} M NDGA (Tappel and Marr, 1954). Acute toxicity studies indicated that the guinea pig is more sensitive than the rat (Griepentro, 1961). Published, long-term studies in the rat and mouse provided little detailed information and left some of the investigators in doubt regarding its safety (Cranston et al., 1947; Mannell, 1964).

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Nuts

see Almonds and Walnuts Albert et al. (2002) prospectively assessed whether increasing the frequency of nut consumption was associated with a lower risk of sudden cardiac death and related coronary heart disease points among 21,454 males enrolled in the U.S. Physicians' Health Study. Participants were monitored over an average of 17 years, and the results suggested an inverse association between nut consumption and the total coronary heart disease deaths.

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O

Oatmeal

Using a lauryl sulfate-irritation model, Boyer and coworkers (1998) demonstrated the anti-inflammatory and healing properties of several processed oatmeal extracts from *Avena Rheala* and *Avena Sativa*. Incorporating 20 percent of each oatmeal extract in a petrolatum ointment resulted in a similar 60 percent inhibition of perfusion blood flow, a measure of inflammation following application of 50 µl of 1 percent solution of lauryl sulfate to the forearm of 12 healthy volunteers, compared to the control. Oatmeal is recommended by veterinarians for treating skin allergies in pets.

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Oats

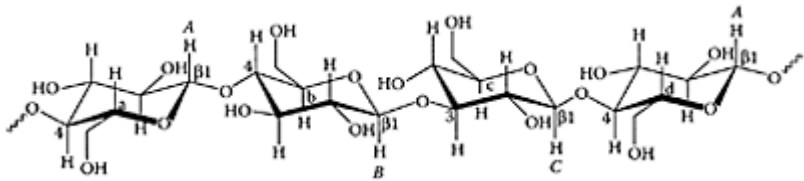
The first health claim permitted by the Food and Drug Administration (FDA) in the U.S.A. under the Nutrition Labelling and Education Act (1990) for a specific food was made for diets high in oatmeal, oat bran, or oat flour. These diets were associated with a reduction in coronary heart disease. Food and feed oats belong to the species *Avena sativa*. Katz et al. (2001a) was the first to report the beneficial effects of daily supplementing the diet of 50 healthy subjects with whole-grain oats or wheat cereal by ameliorating the fat-induced impairment of vascular reactivity. The results observed were comparable to that of vitamin E. In fact, endothelial dysfunction following acute fat ingestion was shown by Katz et al. (2001b) to be concomitant with ingestion of vitamin E and oats, but not wheat.

The reduction in blood-cholesterol levels by oats was attributed to the presence of high levels of soluble fiber in the bran. This proved to be a linear, high-molecular-weight β -

glucan, composed of β -1,4-linked glucose units separated by a single β -1,3-linked glucose every two or three units (Braaten et al., 1999).

Behall and coworkers (1997) examined the hypolipidemic effects of this soluble fiber by incorporating it into a typical diet of 7 men and 16 women. They found that β -glucan reduced total and LDL cholesterol, particularly in subjects maintained on a high β -glucan diet (Table O.49). No changes in triacylglycerol levels were observed.

Using a randomized, blind, placebo-controlled crossover design, Braaten et al. (1999) further established the relationship between oat-bran consumption and reduction in blood cholesterol in hypercholesterolemic individuals. Davy et al. (2002) showed that the addition of two large servings of oats also significantly reduced total and LDL cholesterol, thereby reducing the risk of cardiovascular disease.



Oat mixed-linkage β -glucan [(163)(164)- β -D-glucan. (From Colleoni-Sirghie et al., *Carbohydr. Polym.*, 54:237–249, 2003. With permission.)

TABLE O.49
Mean Plasma Lipids in Subjects on Controlled Diets

	Maintenance diet mmol/L	Low β -glucan diet (1 percent)	High β -glucan diet (1 percent)
Total Cholesterol	5.47±0.19	4.95±0.19	4.67±0.19
LDL Cholesterol	3.65±0.16	3.11±0.16	2.89±0.16

Source: From Behall et al., *J. Am. Coll. Nutr.*, 16:46–51, 1997. With permission.

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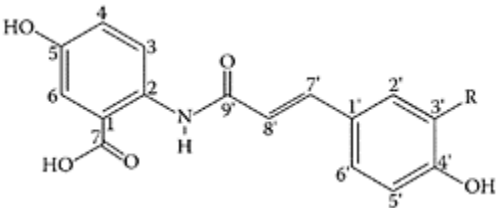
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Oat avenanthramides

A group of novel alkaloids containing phenolic groups was identified by Collins (1989) in oat groats and hulls and identified as avenanthramides. They are substituted hydroxycinnamic-acid conjugates, with more than 25 types identified. The three most abundant avenanthramides, *N*-(4'-hydroxy-3'-cinnamoyl)-5-hydroxy-anthranilic acid (Bf), *N*-(4'-hydroxycinnamoyl)-5-hydroxy-anthranilic acid (Bp), and *N*-(3',4'-dihydroxycinnamoyl)-5-hydroxyanthranilic acid (Bc), were shown to exhibit antioxidant activity using two *in vitro* systems (Scheme O.40) (Peterson et al, 2002). The levels of avenanthramides in oat groats were shown by Emmons and Peterson (2001) to be affected by genotype and growing conditions. Further breeding or growing in a particular environment could enhance the antioxidant capacity. Ji et al.



Avenanthramide	R
Bp	H
Bf	OCH ₃
Bc	OH

SCHEME O.40 Oat aventhramides Bc, Bp, and Bf structures. (Peterson et al., *Food Chem.*, 79:473–478, 2002. With permission.)

(2003) showed for the first time that a diet supplemented with 0.1 percent synthetic Bc was tissue specific by only attenuating exerciseinduced ROS in the soleus muscle and lipid peroxidation in the heart of female SpragueDawley rats compared to the control. A

recent study by Liu and coworkers (2004) provided further evidence for the anti-inflammatory and antiatherogenic properties of oat avenanthramides.

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Ocimum sanctum

Ocimum sanctum, an annual herb grown throughout India, is considered sacred by the Hindus as *tulsi*, or “holy basil” in English. It has been reported to possess therapeutic properties, such as anticarcinogenic, antiseptic, antirheumatic, antistress, antihelmintic, and antibacterial activities (Bhargava and Singh 1981; Singh et al., 1996; Singh and Majumdar, 1999; Godhwani et al., 1987, 1988). Singh and Majumdar (1997) attributed the antiinflammatory activity of *O. sanctum* to the ability of linolenic acid present in the fixed oil to block both the cyclooxygenase and lipoxygenase pathways of arachidonate metabolism. In addition to anti-inflammatory properties, Singh and Majumdar (1999) also reported *O. sanctum*-fixed oil had antiulcer activity. A recent study by Dharmani et al. (2004) confirmed the antiulcer and ulcer-healing properties of *O. sanctum*. Using acetic acid-induced chronic gastric-ulcer animal models, they found the ulcers were completely healed within 20 days of treatment. They attributed this effect to the cytoprotective properties of *O. sanctum*, which has considerable potential for treating peptic ulcers.

Using an anaesthetized dog, Singh et al. (2001) showed the oil from *O. sanctum* exhibited hypotensive and anticoagulant activities comparable to that of aspirin. The ability of the oil to increase the pentobarbitone-induced sleeping time in rats was attributed to its possible inhibition of the cytochrome system involved in the hepatic metabolism of this drug.

The potential of *O. sanctum* for treating diabetes mellitus was examined by Vats and coworkers (2002), using an ethanolic extract from its leaves. They found a small but significant hypoglycemic effect in normal rats, as a single administration of 100, 200, and 400 mg/kg of the extract decreased glucose levels by 7.64 percent, 17.18 percent, and 19.78 percent, respectively. A significant reduction in plasma glucose levels was also observed in alloxanized rats. Recent work by Vats et al. (2004) showed *O. sanctum*

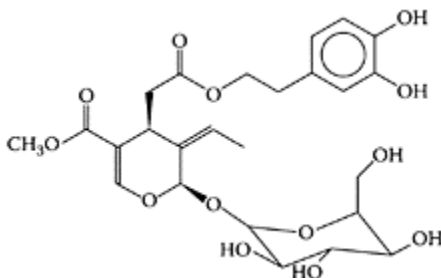
significantly increased the activity of glucokinase, hexokinase, and phospho-fructokinase, the three key enzymes of carbohydrate metabolism, in streptozotocin-induced rats. The increase in these glycolytic enzymes observed in animals treated with *O. sanctum* could be secondary to the release of insulin. Since streptozotocin diabetes is an insulin-deficient model, it is likely that the component in *O. sanctum* exerts insulinomimetic activity. Further clinical studies are needed, however, to more conclusively establish *O. sanctum* as an antidiabetic herb. An earlier *in vitro* study by Halder et al. (2003) showed that the anticataract properties of an aqueous extract from *O. sanctum* was a significant inhibitor of aldose reductase in the rat lens. The latter enzyme plays a key role in sugar-induced cataract formation.

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Oleuropein

Oleuropein is a polyphenolic glycoside constituent in the leaves, fruit, and oil of olives (*Olea europaea*) responsible for the bitter taste of olives (Panizzi et al., 1960). Its ability to inhibit platelet aggregation induced by arachidonic acid and adenosine diphosphate was first reported by Petroni et al. (1995). The effect of Oleuropein on the platelet-activating factor (PAF), the third and most potent pathway



Oleuropein. (From Furneri et al., *Int. J. Antimicrob. Agents*, 20:293–296, 2002. With permission.)

causing platelet aggregation, was investigated by Andrikopoulos and coworkers (2002). Addition of 10 μ M oleuropein, a level equivalent to the average intake of olive oil or olive pieces in the Mediterranean diet, reduced *in vitro* oxidation of LDL cholesterol by total polar compounds formed during oil frying by approximately 50 percent. Oleuropein also inhibited human-plasma aggregation irrespective of its induction by arachidonic acid, adenosine diphosphate, or PAF. These results suggested oleuropein could play a role in the prevention of atherogenic plaques and thus reduce the risk for cardiovascular disease. The first experimental evidence for the direct cardioprotective effect of oleuropein following coronary occlusion was reported recently by Manna and coworkers (2004). The antioxidant properties of oleuropein appeared to prevent postischemic oxidative burst by reducing the amount of oxidized glutathione, a sensitive marker of the heart's exposure to oxidative stress. The presence of oleuropein also reduced lipid-membrane peroxidation by reducing thiobarbituric acid reactive substances in cardiac tissue after ischemia/reperfusion of isolated rat hearts (Figure O.70).

Oleuropein also inhibited or delayed the growth of a number of bacteria and microfungi (Tranter et al., 1993; Capasso et al., 1995;

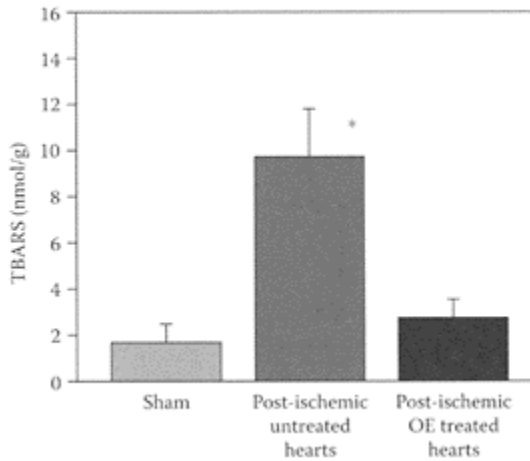


FIGURE O.70 Effect of oleuropein (OE) on thiobarbituric-reactive substance (TBARS) formation in the cardiac tissue after ischemia/reperfusion of isolated rat hearts. Isolated hearts were subjected to 30 min of global ischemia and then reperused. After 1 h of reperfusion, hearts were removed from the perfusion apparatus and TBARS measured. Data (mean \pm SD; n=6) were analyzed by the Student t test. * p <0.05 compared to SHAM samples. (Manna et al., *J. Nutr. Biochem.*, 15:461–466, 2004. With permission.)

Tassou et al., 1995). Bisignano et al. (1999) reported oleuropein exhibited antimicrobial activity against the human pathogenic bacteria ATTC and clinically isolated Gram-positive and Gram-negative strains of *Salmonella* spp., *Vibrio* spp., and *Staphylococcus aureus*. Further work by Furneri et al. (2002) confirmed the *in vitro* antimycoplasmal activity of oleuropein by its inhibition of *Mycoplasma fermentans* and *Microplasma hominis* strains. The latter are normally resistant to erythromycin and very often to tetracyclines. However, further research is needed to determine whether oleuropein retains its antimycoplasmal properties *in vivo*.

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Oligofructose

see also Inulin, Prebiotics Oligofructose, a nondigestible carbohydrate composed of fructose units, including inulin, provide a number of benefits, such as constipation relief (Den Hond et al., 2000), prebiotics (Gibson et al, 1995), stimulation of calcium absorption from food (Van den Heuvel et al., 1999), and cancer prevention (Taper et al., 1998; Reddy et al., 1997).

The prebiotic nature of Oligofructose was demonstrated by Rao (2001), who fed eight healthy subjects 5 g/day of Oligofructose over three weeks compared to an equivalent amount of sucrose. Consumption of this low dose of oligosaccharides caused a one-log cycle increase in bifidobacterium after 11 days, indicative of an improved fecal-bacteria composition. A quantitative approach by Vulevic et al. (2004) derived an equation for measuring the prebiotic effect (MPE) of dietary fructooligosaccharides that included the production of lactic acid, as well as short-chain fatty acids (SCFA), acetic, propionic, and butyric acids. The production of SCFA, such as the propionate/acetate ratios, was reported to affect plasma glucose and lipid metabolism (Todesco et al., 1991; Boillot et al., 1995). Giacco and coworkers (2004) found that a moderate intake of short-chain fructooligosaccharides (10.6 g/day) by subjects with mild hypercholesterolemia, had no clinically relevant effect on either glucose or cholesterol levels, both at fasting or in the

postprandial period. However, a small but significant increase was observed for Lp(a) levels, together with a reduction in postprandial insulin response.

Kelly-Quagliana and coworkers (2003) found that Oligofructose and inulin both modulated immune function in mice by increasing the level of natural killer (NK) cell activity of splenocytes and phagocytic activity of peritoneal macrophages. Both upregulated the macrophage-dependent immune responses in a dose-dependent manner.

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Oligosaccharides

see Oligofructose and Inulin

Olives

see also Hydroxytyrosol and Oleuropein Olives are oval fruits composed of water, oil, sugar, protein, organic acids, and cellulose. The oil, which accounts for around 20 percent of the olive, is located mainly in the pulp. In addition to being a rich source of the monounsaturated fatty acid oleic acid, olives also contain large amounts of polyphenols, of which the secoiridoid glycoside oleuropein is the most abundant. The latter is composed of elenolic acid (oleoside-11-methylester) and hydroxytyrosol (3,4-dihydroxyphenyl ethanol) (Blekas et al., 2002). Oleuropein is responsible for the very bitter taste of unprocessed olives and is normally eliminated prior to human consumption by lye treatment or fermentation. Nevertheless, oleuropein has been shown to enhance nitric-oxide production in mouse macrophages, considered beneficial for the protection of the organism (Visioli et al. 1998). During ripening, oleuropein is hydrolyzed to smaller molecules, such as hydroxytyrosol, which gives extra-virgin oil its rich and complex flavor. Other phenolics reported in unprocessed olives include ligstroside (ester of elenolic acid with 4-hydroxyphenyl ethanol or tyrosol) and hydroxycinnamic acids, caffeic and ferulic.

The beneficial effects of olive oil are not only due the presence of monounsaturated fatty acids but also to the antioxidant properties of polyphenols in the oil. Hydroxytyrosol (3,4-dihydroxyphenyl) ethanol (DHPE), which accounts for 70–80 percent of total phenols in extra-virgin olive oil, was shown to be a very effective scavenger of peroxy radicals, protecting human erythrocytes from oxidative damage (Manna et al., 1998). In addition to tyrosol and hydroxytyrosol, Bonoli et al. (2003) identified a number of other phenolic compounds in olive oil by capillary-zone electrophoresis, including 2,3-dihydroxyphenylethanol. The lower incidence of cardiovascular disease was attributed to their contribution in the Mediterranean diet. Olive polyphenols have also been associated with a lower incidence of some cancers (Trichopoulou, 1995; Trichopoulou et al., 2000). Visioli and Galli (2003) recently reviewed the waste products of olives as sources of bioactive compounds for the treatment of chronic diseases.

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Omega-3 fatty acids

see also Eicosapentaenoic and Docosahexaenoic acids Omega3 fatty acids belong to the family of long-chain polyunsaturated fatty acids with the first double bond located at the third carbon from the terminal methyl end of the molecule between carbons three and four. They are the precursors of prostaglandins, thromboxanes, and leukotrienes, chemical messengers that control a number of important biochemical processes, including cell growth and division, blood pressure and clotting, immune reactions, and inflammation. The essential fatty acid, α -linolenic acid (C18:3 ω 3), is the precursor of eicosapentaenoic acid (EPA) (C20:5 ω -3) and docosahexaenoic acid (DHA) (C22:6 ω -3). It has been suggested that 1.5 percent of the daily total calories should be derived from omega-3 fatty acids (3 g for men and 2 g for women) or EPA and DHA (1.4 g for men and 1.2 g for women). The richest sources of omega-3 are fish oils, such as herring, mackerel, sardines, and salmon (Eskin, 2002). To meet these levels requires eating three (200–300 g) portions per week of these fatty fish. Increasing omega-3 intake is important for individuals with a family history of heart or circulatory problems. Omega-3 fatty acids reduce the risk of heart attacks by reestablishing a more normal lipid profile among people with hypertriglyceridemia. Eritsland et al. (1995) reported a 19 percent reduction in triglyceride levels when fed 4 g of fish. Epidemiological studies suggest that in societies where diets are high in fish, heart attacks, strokes, and circulatory problems are relatively rare. A 20-year study in the Netherlands by Simon (1994) showed that men who ate 30 g of fish daily were half as likely to die from coronary heart disease. Lau et al. (1993) also found that treating rheumatoid arthritis sufferers with supplements containing EPA (171 mg) and DHA (114 mg) reduced the amount of nonsteroidal, anti-inflammatory drugs (NSAIDs) needed. A marked improvement was observed after a year, in which there was a significant reduction in tender-joint counts and morning stiffness compared to the control group. This was confirmed in a later study by Kremer et al. (1995). The level of interleukin1 β decreased significantly in patients consuming fish oils, suggesting omega-3 fatty acids reduced the underlying disease process. Other areas in which omega-3 fatty acids appear to play a beneficial role include possible protection to smokers against chronic obstructive pulmonary disease (COPD). Britton (1995) postulated that omega-3 fatty acids reduce prostaglandin and leukotriene synthesis, inhibit migration of proinflammatory neutrophils into the lung, and reduce the lung's response to allergens. The importance of omega-3 fatty acids in the synthesis of prostaglandins and other inflammatory mediators led to their role in other inflammatory disease. For example, fish oils have been shown to lessen itching and inflammation in psoriasis, while essential fatty acids exert anti-inflammatory action in infantile seborrheic dermatitis and diaper dermatitis. A recent application is the possible use of omega-3 fatty acids for reducing the relapse in the inflammatory disease of the GI tract, Crohn's disease.

Epidemiological and experimental evidence suggests that omega-3 fatty acids exert a protective effect against common cancers, most notably breast and colon (Rose and Connolly, 1999; Klein et al., 2000; Maillard et al., 2002). Animal studies provided convincing evidence that omega-3 fatty acids inhibited mammary-tumor growth and metastasis. Hardman (2002) reviewed the evidence for omega-3 fatty acids as an anticancer agent, suggesting it may augment cancer therapy. Kato and coworkers (2002) showed dietary omega-3 fatty acids exerted significant tumorsuppressing activities on the growth of human colon carcinoma xenograft in athymic nude mice. The primary tumor-suppressing acid was found to be docosahexaenoic acid.

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Onions (*Allium cepa* Liliaceae)

Onions are one of the major sources of flavonoids in the Western diet (Knekt et al., 1996). They are particularly rich in quercetin, and its glycosides have been used in

traditional medicine for their antiasthmatic, antithrombotic, antihypertensive, antihyperglycemic, antihyperlipidemic, and antitumor properties (Bordia et al., 1975, 1977; Belman, 1983; Dorsch et al., 1985; Kleijnen et al., 1990; Wagner et al., 1990). These health benefits are attributed to the presence of flavonoids and alk(en)yl cysteine sulphoxides in onions (Griffiths et al., 2002).

In vitro studies by Glasser et al. (2002) showed quercetin, a flavonoid in onion, inhibited hepatic cholesterol biosynthesis. Kumari and Augusti (2002) found (+)-S-methyl-L-cysteine sulfoxide in onion exhibited antidiabetic and antioxidant activities comparable to standard drugs. However, Ali and coworkers (2000) found onion extracts ineffective in lowering serum cholesterol in rabbits kept on a cholesterol-supplemented diet compared to garlic.

The presence of quercetin, alkyl sulfides, and diallyl disulfide in onions suggested it had strong anticancer properties. Seki et al. (2000) found that both onions and garlic equally suppressed the growth of leukemia HL-60 cells. Hu and coworkers (1999) reported an inverse relationship between onions in the diet and the risk of brain cancer. Shon and coworkers (2004) found the antioxidant and antimutagenic activities of ethyl-acetate extracts from red, yellow, and white onion extracts could be attributed to the presence of phenols and flavonoids.

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Oolong tea (*Camelia sinensis*)

Oolong tea, one of three types of tea manufactured from tea leaves, is considered a functional food because of its antioxidant, hypocholesterolemic, and antiobesity properties (Yang and Koo, 1997; Benzie and Szeto, 1999; Han et al, 1999). It is produced from green tea by heating and fermentation and contains more than 70 different compounds, such as oolonghomobisflavan A, B¹, and theasinensin, formed from epigallocatechin gallate. Mihara and coworkers (2004) recently identified a novel acylated quercetin tetraglycoside in oolong tea extracts, 3-*O*-(2^G-*p*-coumaroyl-3^G-*O*-β-L-arabinosyl-3^R-*O*-D-glucosylrutinoside (compound 1). These researchers also found that compound 1 was a good antioxidant but not quite as strong as quercetin (Table O.50). Unlike quercetin, the acylated quercetin tetraglycoside (compound 1) was soluble in water, which suggested it might be a better antioxidant, as it would be absorbed more easily.

Yang and coworkers (2001) compared green-, oolong-, and black-tea extracts for their ability to modulate lipid metabolism in hyperlipidemia rats maintained on a high-sucrose diet. Oolong tea reduced food intake, while both oolong and black teas significantly decreased body weight gain and food efficiency. Although green and oolong teas had similar catechins, green tea still exerted a greater antihyperlipidemic effect. Kuihara et al. (2002) showed oolong tea alleviated the stress-induced

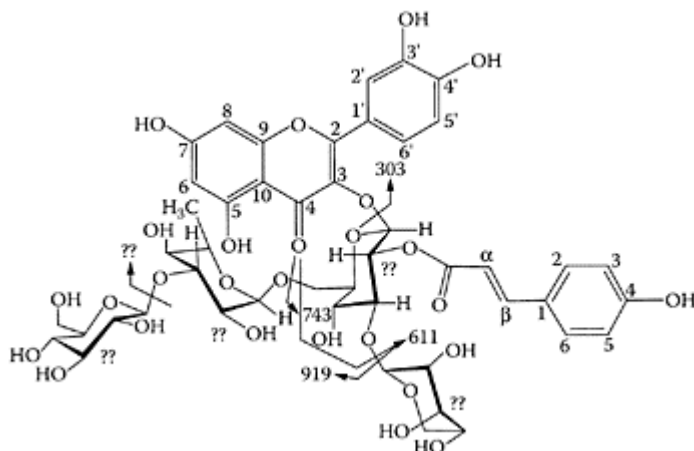
TABLE O.50 Antioxidant Activity of Compound 1

	EC ₅₀ (nmol/mL) ¹
Compound 1	16.2
Quercetin	8.6
<i>p</i> -Coumaric acid	377.8
α-Tocopherol	27.4

¹ The effective concentration of antioxidant needed to decrease the initial DPPH radical by 50

percent.

Source: From Mihara et al., *Tetrahedron Lett.*, 45:5077–5080, 2004. With permission.



Compound 1. (From Mihara et al., *Tetrahedron Lett.*, 45:5077–5080, 2004. With permission.)

decrease in the rate of blood-lipid metabolism in mice. Reduction in plasma-triacylglycerol levels by oolong tea in the stressed mice was attributed to the antistress and antioxidant properties of its polyphenols and saponins, theasaponins E1 and E2 (Okuda and Han, 2001).

Shimada et al. (2004) demonstrated, for the first time, that long-term intake of oolong tea (one month) significantly ($p < 0.05$) increased plasma adiponectin levels from $6.26 \pm 3.26 \mu\text{g/mL}$ to $6.88 \pm 3.28 \mu\text{g/mL}$ in patients suffering from coronary artery disease. Adiponectin, a collagen-like plasma protein produced by adipose tissue normally abundant in circulation, is reduced in patients suffering from obesity, type 2 diabetes mellitus, and coronary artery disease (Matsuzawa et al., 1999; Ouchi et al., 1999; Hotta et al., 2000). A significant ($p < 0.01$) increase in LDL particle-size plasma levels from $25.02 \pm 0.67 \text{ nm}$ to $25.31 \pm 0.60 \text{ nm}$ was also observed. These effects could slow down the progression of atherosclerosis, as plasma level LDL particle sizes were shown previously to be lower in patients with coronary artery disease and associated with the etiology of the disease (Lamarche et al., 1998).

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Oranges

see Orange Juice

Orange juice

see also Hesperidin, Nobiletin, and Tangeretin Besides being an excellent source of provitamin A carotenoids, orange juice is rich in antioxidant carotenoids. Many of these carotenoids appear to play a role in the reduction of degenerative diseases, such as cancer and heart disease. These include β -carotene, α -carotene, and β -cryptoxanthin, as well as zeaxanthin and lutein. Using the 2,2-diphenyl-1-picrylhydrazyl stable radical-scavenging method, Sanchez-Moreno et al. (2003) found vitamin C was the largest contributor to the antioxidant potential of orange juice, followed by flavonoids and carotenoids.

TABLE O.51 Effect of Orange Juice on Plasma Lipids

Variable	Dietary Period				
	Baseline	1	2	3	Washout
Plasma cholesterol (mmol/L)					
Total	6.3±1.0	6.4±0.9	6.5±1.0	6.5±0.9	6.3±1.0
VLDL	0.8±0.4	1.0±0.6	0.8±0.4	0.9±0.4	0.8±0.4
LDL	3.6±0.7	3.8±0.6	3.7±0.7	3.6±0.7	3.5±0.7
HDL	1.0±0.3	1.0±0.3	1.1±0.3	1.2±0.31	1.3±0.4 ¹
Change in HDL (percent)	0	5	7	21	27
LDL:HDL cholesterol	3.8±0.9	3.8±0.9	3.6±1.0	3.1±0.9 ¹	3.0±1.0 ¹
Change in LDL:HDL cholesterol (percent)	—	0	−4	−16	−20
Total triacylglycerol (mmol/L)	1.6±0.7	1.9±1.0	1.8±0.8	2.0±0.9 ¹	1.7±1.0

¹ Significantly different from baseline, $p < 0.05$ (ANOVA followed by Dunnett's test).

Source: From Kurowska et al., *Am. J. Clin. Nutr.*, 72:1095–1100, 2000.

The hypocholesterolemic effect of soybean was attributed to the flavonoid genistein (Anthony et al., 1996). The similarity in structure between genistein and hesperetin in oranges may also make orange juice hypocholesterolemic. This was confirmed by Kurowska and coworkers (2000), who showed a daily minimum consumption of 750 mL of orange juice by hypercholesterolemic individuals significantly increased HDL-cholesterol concentrations by 21 percent and the LDL-HDL cholesterol ratio by 16 percent. No change was observed for LDL-cholesterol and homocysteine levels, while triacylglycerol levels increased 30 percent from 1.6 to 2.0 mmol/L (Table O.51).

Ikegawa et al. (2000) also demonstrated the ability of orange-juice components to inhibit P-glycoprotein in adriamycin-resistant human myelogenous leukemia (K562/ADM) cells. P-glycoprotein acts as an energy-dependent drug efflux pump, decreasing the intracellular drug accumulation and the therapeutic effect of many chemotherapeutic agents. All three orange-juice components, tangeretin, nobiletin, and heptamethoxyflavone (HMF), were found to reverse the multidrug resistance (MDR) without inhibiting CYP-3A4.

Sprecher and coworkers (2002) reported a positive effect of dietary intervention of not-from-concentrate orange juice to 24 nondiabetic patients with angiographic CAD on vascular regulation, which could affect health strategies for reducing blood pressure. A study by Lilja and coworkers (2004) noted that orange juice reduced the bioavailability of celiprolol, a β -adrenergic-blocking agent with vasodilating properties. The negative impact of orange juice with celiprolol must be avoided by patients on this drug.

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Oregano (*Origanum vulgare* L.)

Oregano, an aromatic perennial herb, is a member of the *Labiatae* family. The oil from oregano is used for its fragrance in perfumes and for its flavor in seasonings. Health benefits associated with oregano have been attributed to antioxidants in its essential oil and soluble phenols (Engleberger et al., 1988; Peak et al., 1991; Eguchi et al., 1996). Kikuzaki and Nakatani (1988) identified rosmarinic acid as one of the major phenolic compounds in the methanolic extract of oregano leaves. The latter has been reported to exert both antioxidant and anti-inflammatory properties. The variability in the phenolic content of oregano, however, has limited it as a functional food. To overcome the problem of genetic heterogeneity of oregano, clonal selection has been used to ensure consistency in phenolic quantity and quality. Chun et al. (2005) compared a high phenolic clonal line of oregano developed at the University of Massachusetts with a purchased commercial heterogenous line. The clonal line was much higher in total phenolics and antioxidant activity, as well as improved antimicrobial activity against *Helicobacter pylori*, an organism associated with ulcers. The development of high phenolic clonal oregano lines could provide useful functional-food sources of oregano for combating chronic bacterial infections.

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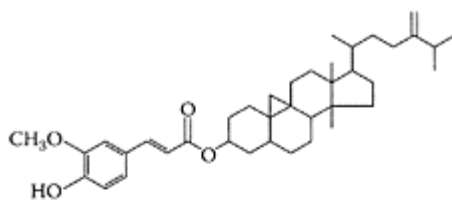
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γ -Oryzanol

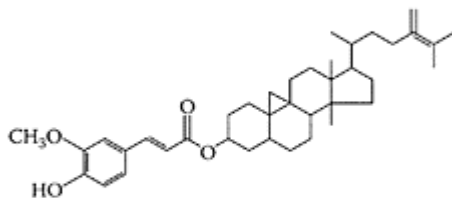
γ -Oryzanol is a mixture of sterol esters of ferulic acid, found in rice-bran oil (Rogers et al., 1993).

The highest concentration of γ -oryzanol was recently extracted from the rice bran during the shorter milling duration (Rohrer and Siebenmorgen, 2004). Studies showed it lowered blood cholesterol in rats and that the addition of 0.5 percent γ -oryzanol to a cholesterolenriched diet effectively reduced triacylglycerols, LDL cholesterol, and VLDL cholesterol in the serum, and cholesterol in the liver (Nicolosi et al., 1993; Seetharamaiah and Chandrasekhara, 1993). In addition, γ -oryzanol was also an effective antioxidant, protecting ricebran oil from oxidation by iron or UV radiation (Jariwalla et al., 2001). Of the three major γ -oryzanol derivatives in rice bran, 24-methylenecycloartanyl ferulate exhibited the highest antioxidant activity compared to cycloartanyl ferulate or campestryl ferulate.

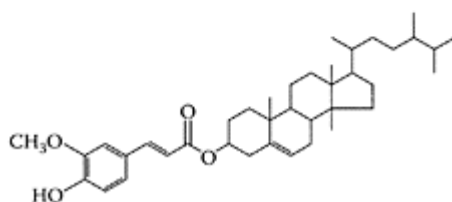
All three compounds were much stronger antioxidants than any of the vitamin E isomers (Xu et al., 2001). Earlier *in vitro* tests showed γ -oryzanol had superoxide dismutase-like antioxidant activity (Kim et al., 1995). A review by Cicero and Gaddi (2001) discusses some of the health claims made for γ -oryzanol, as well as the pharmacology and toxicology of rice-bran oil.



24-Methylene cycloartanyl ferulate



Cycloartanyl ferulate



Campesteryl ferulate

Three major γ -oryzanol derivatives in oats. (From Xu et al., 2001. With permission.)

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Ovakinin

Ovakinin (2–7) is a novel, antihypertensive peptide produced from ovalbumin by chymotryptic digestion (Matoba et al., 2000). Yamada and coworkers (2002) showed that replacing the C-terminal Phe residue with Tryp improved the antihypertensive activity of ovakinin.

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Oyster mushroom (*Pleurotus ostreatus*)

Oyster mushroom is a wood-rotting fungus produced industrially for the food industry on lignocellulose substrates. A pilot study by Bobek and coworkers (1993) showed that oyster mushrooms suppressed diet-induced hypercholesterolemia in rats. The mechanisms responsible were shown to be reduced cholesterol absorption and increased excretion of plasma cholesterol (Bobek et al., 1994), reduced activity of 3-hydroxy-3-methylglutaryl CoA reductase, a key enzyme in cholesterol

TABLE O.52 Inhibition of Sarcoma 180 or Hepatoma 22 Growth by POL

Tumor		Control Group (n=8)	Lectin-Treated Group (n=8)
Sarcoma	Tumor weight (g)	0.5774±0.0430	0.0667±0.0021 (p<0.002)
S-180	% Inhibition of tumor growth		88.46
Hepatoma	Tumor weight (g)	0.9928±0.1242	0.2439±0.0004 (p<0.002)

H-22	% Inhibition of tumor growth	75.42
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Source: From Wang et al., *Biochem. Biophys. Res. Commun.*, 275:810–816, 2000. With permission.

biosynthesis (Bobek et al., 1995), and a reduction in the production and secretion of verylow-density lipoproteins (VLDL) in hypercholesterolemic rats (Bobek and Ozdin, 1996). Long-term feeding of 5 percent oyster mushrooms to rats by Bobek et al. (1998) significantly reduced serum (31–46 percent) and liver (25–30 percent) cholesterol during the eighth and 28 weeks of feeding. In addition to lowering VLDL, there was a decrease in conjugated dienes in erythrocytes and an increase in reduced glutathione in the liver, accompanied by enhanced catalase and glutathione-peroxidase activity during the last period of the study.

Wang et al. (2000), using a simple procedure, isolated a lectin (POL) from the freshfruiting bodies of the edible oyster mushroom (*Pleurotus ostreatus*) that exhibited strong antitumor activity. It proved to be a dimeric lectin composed of two subunits with molecular weights of 40 and 41 kDa, respectively. It was a potent inhibitor of sarcoma S-180 and hepatoma H-22 growth, as evident in Table O.52.

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P

Palatinose®

Palatinose® is the commercial product isomaltose, obtained from sucrose by enzymatic rearrangement followed by crystallization (Scheme P.41). It is found naturally in honey (Barez et al., 2000) and products derived from sugar-cane juice, such as treacles and molasses (Takazoe, 1985). Unlike sucrose, a nonreducing disaccharide in which glucose and fructose are linked α -1,2, isomaltose is a reducing disaccharide in which glucose and fructose are linked α -1,6. As a result, palatinose is hardly fermented by oral microbes and appeared to be a suitable noncariogenic sucrose replacement for incorporation into products for diabetics (Kawai et al., 1989).

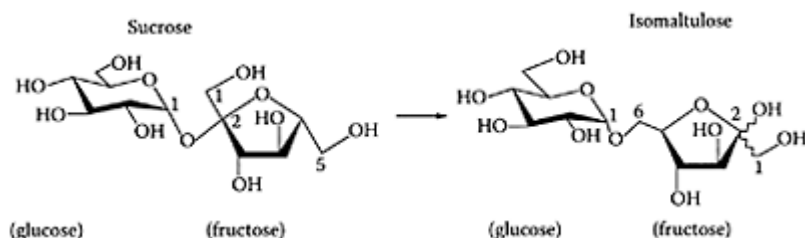
In vivo studies with rats and pigs showed it is completely hydrolyzed and absorbed in the small intestine. However, the rate of hydrolysis was very slow compared to sucrose or maltose so that in humans the rise of blood glucose and insulin levels after oral administration was slower, reaching lower maxima compared to sucrose. No embryotoxic or teratogenic effects were observed in rat fetuses, nor maternal toxicity at levels up to 7 g/kg body weight/day (Lina et al., 2002). Using the Ames test, they found isomaltose was nonmutagenic and was a safe alternative sugar. Dietary levels of up to 10 percent isomaltose were shown by Jonker et al. (2002) to be well tolerated without any signs of toxicity. The overall intake at this level corresponded to 7.0 and 8.1 g/kg body weight/day in male and female rats, respectively.

Although palatinose appears to be a noncariogenic disaccharide and unable to be utilized by *Streptococcus mutans*, Matsuyama et al. (2003) showed there were still a significant number of bacteria in dental plaque capable of fermenting it. Using the Uchida-Kraepelin psychodiagnostic test, Kashimura et al. (2003) found that 5 g of palatinose enhanced mental concentration by increasing calculation ability.

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SCHEME P.41 Enzymatic rearrangement of sucrose to isomaltulose. (From Lina et al., *Food Chem. Toxicol.*, 40:375–381, 2002. With permission.)

Lina, B.A., Jonker, D., and Kozianowski, G., Isomaltulose (Palatinose®): A review of biological and toxicological studies, *Food Chem. Toxicol.*, 40:375–381, 2002.

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Palmetto berries

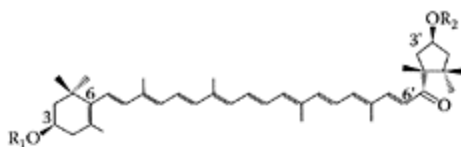
Palmetto berries are obtained from Saw palmetto, an herbal product used to treat symptoms related to benign prostatic hyperplasia. Studies demonstrated the effectiveness of saw palmetto in reducing symptoms associated with benign prostatic hyperplasia (Ernt, 2002; Gordon and Shaughnessy, 2003) and lower urinary-tract symptoms (Wilt et al., 1998; Koch, 2001). The mechanism whereby saw palmetto improves urinary symptoms is unknown (Gerber et al., 2001). There are no known drug interactions with saw palmetto, with reported side effects extremely rare. A six-month study of forty-four men with benign prostatic hyperplasia with a Saw palmetto herbal by Veltri et al. (2002) found an alteration in DNA chromatin structure and organization of prostate epithelial cells. Goldman et al. (2001) reported inhibition of proliferation of a set of prostatic cell lines when dosed with Saw palmetto-berry extract (SPBE) for three days. Reduced cellular activity appeared to be related to decreased expression of COX-2 and possible changes in the expression of Bcl-2. Since an increase in COX-2 expression is associated with an increase in incidence of prostate cancer, its reduction by SPBE suggests its possible use against benign prostatic hyperplasia and in prostate-cancer prevention. Talpur et al. (2003) showed whole berry and extracts of Saw palmetto influenced hyperplasia via androgen metabolism.

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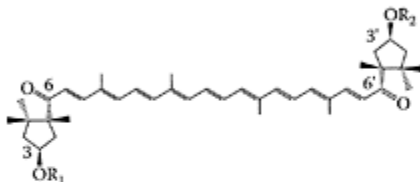
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Paprika (*Capsicum annuum* L.)

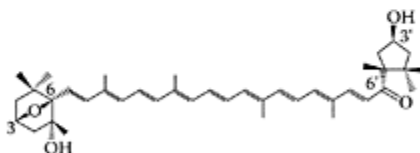
Carotenoids have been reported to play a role in the prevention of cancer. Oshima et al. (1997) showed that capsanthin, a major carotenoid in paprika (*Capsicum annuum*), was absorbed into the body following ingestion of paprika juice. In addition to capsanthin, 11-*cis*-capsanthin was also identified and could also be important to human health. Narisawa et al. (2000) reported that paprika juice rich in capsanthin (3.54 mg/100 mL) inhibited *N*-methylnitrosourea-induced colon carcinogenesis in F344 rats. Etoh and coworkers (2000) also reported the absorption of paprika carotenoids following ingestion of paprika juice. The red pigments in paprika, capsanthin, capsorubin, and capsanthin 3,6-epoxide, all possess 3-hydroxy- κ -end groups (Scheme P.42). The antitumor activity of isolated paprika



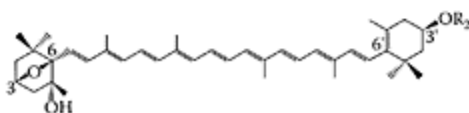
Capsanthin (1): $R_1 = H$, $R_2 = H$
 Capsanthin 3'-ester(2): $R_1 = H$, $R_2 = \text{Acyl}$
 Capsanthin 3, 3'-diester(3): $R_1 = \text{Acyl}$, $R_2 = \text{Acyl}$



Capsorubin (4): $R_1 = H$, $R_2 = H$
 Capsorubin 3, 3'-diester(5): $R_1 = \text{Acyl}$, $R_2 = \text{Acyl}$



Capsanthin 3, 6-epoxide(6)



Cucurbitaxanthin A 3'-ester (7): $R = \text{Acyl}$

Structures of capsanthin and related paprika carotenoids. (From Maoka et al., *Cancer Lett.*, 172:103–109, 2001. With permission.)

carotenoids associated with these structures was demonstrated by Maoka and coworkers (2001) using an Epstein-Barr virus early antigen (EBV-EA) activation induced by the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and an *in vitro*, two-stage carcinogenesis assay on mouse skin using 7,12-dimethylbenz[*a*]anthracene as an initiator and promoter. Strong, antitumor promoting activities were observed for capsanthin and related paprika carotenoids without any significant cytotoxicity to the Raji cells in this assay. Inhibitory activity increased with esterification of the hydroxyl groups with fatty acids, as evident by the increase in inhibitory activity ranging in the order of capsanthin>capsanthin 3' ester> capsanthin diester>capsorubin diester. This was also evident for inhibition of TPA-induced tumor promotion by capsanthin, capsanthin 3,3"-diester, as shown in Figure P.71.

Sappanen and Csallany (2002) reported *in vivo* antioxidant effects in rats fed vitamin E-deficient diets supplemented with paprika carotenoids (0.5 and 1.0 percent) and β -carotene (1.0 percent) by the lower amount of secondary products from lipid peroxidation

in the urine. While the addition of paprika carotenoids could not compensate for the role of vitamin E in normal growth and weight gain, these oxygenated carotenoids, or xanthophylls, were effective by their *in vivo* inhibition of lipid oxidation. Perez-Galvez et al. (2003) showed the availability of carotenoids from paprika oleoresin by the detection of considerable amounts of zeaxanthin, β -cryptoxanthin, and β -carotene in the chylomicron fraction.

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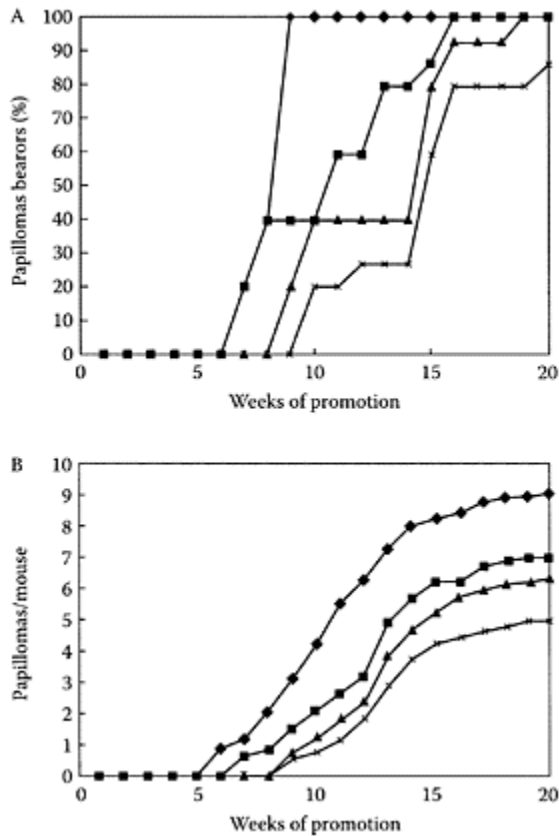


FIGURE P.71 Inhibition of TPA-induced tumor promotion by multiple applications of capsanthin, capsanthin 3' ester, and capsanthin diester. All mice were initiated with DMBA (390 nmol) and promoted with TPA (1.7 nmol) twice weekly starting at one week after initiation. (A) Percentage of mice bearing papillomas; (B) Average number of papillomas per mouse. (◆), Control TPA alone; (■) TPA+85 nmol capsanthin; (▲), TPA + 85 nmol capsanthin 3' ester; (×), TPA+85 nmol capsanthin 3,3'-diester. (From Maoka

et al., *Cancer Lett.*, 172:103–109, 2001. With permission.)

Parsley (*Petroselinium crispum*)

Parsley has a long tradition in folk medicine as a stomachic, carminative, emmenagogue, and abortifacient (Anderson et al., 1996; Robbers and Tyler, 1999; Tyler, 1993). As an herb, it is widely recognized as a diuretic, which could account for its hypotensive properties (Leung, 1980). The mechanism of its diuretic effect appears to be mediated through inhibition of the Na⁺ K⁺ pump that leads to a reduction in Na⁺ and K⁺ reabsorption, resulting in an osmotic water flow into the lumen and diuresis (Kreydiyyeh and Usta, 2002). Earlier work by Kreydiyyeh et al. (2001) confirmed the laxative role of parsley by its inhibition of sodium and subsequent water absorption through its inhibition of the Na⁺K⁺ pump, and by stimulating of the NaKCl transporter and increasing electrolyte and water secretion.

Yoshikawa et al. (2000) found the methanolic extract from the aerial parts of parsley had potent estrogenic activity. This was attributed to several flavone glycosides, including a new flavone glycoside, 6''-acetylapiin, together with a new monoterpene, petroside.

Manderfeld et al. (1997) demonstrated the antibacterial properties of parsley leaves. The photoactive furocoumarins extracted from the leaves inhibited human pathogens, *E. coli* and *Lesteria monocytogenes*, and the spoilage organisms, *Erwinia carotovora* and *Listeria innocua*. Flavones, apigenin, luteolin, and chrysoeriol, and flavonols, quercetin and isorhamnetin, isolated from illuminated parsley-cell suspension culture, increased the antioxidative capacity in the plasma of rats (Hempel et al., 1999). Parsley is one of the medicinal herbs used by diabetics in Turkey and is reported to reduce blood pressure (Tunali et al., 1999).

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Palm oil

Palm oil, a yellowish, fatty oil obtained from the crushed nuts of the African palm (*Elaeis guineensis*), is used in the manufacture of soaps, chocolates, cosmetics, and candles. The oil contains 50 percent saturated fatty acids, 40 percent unsaturated fatty acids, and 10 percent polyunsaturated fatty acids but does not promote atherosclerosis and arterial thrombosis. The saturated to unsaturated fatty acid ratio of palm oil is close to one with oleic acid, predominantly at the sn-2-position in the main triacylglycerols (Ong and Goh, 2002). Palm oil also contains a large amount of antioxidants, β -carotene, and vitamin E (Ebong et al., 1999). The fruit of palm also contains other components that could enhance the nutritional and health benefits. These include phytonutrients, such as sterols (sitosterol, stigmasterol, and campesterol), phospholipids, glycolipids, and squalene. In addition, it was recently reported that water-soluble, powerful antioxidants, phenolic acids, and flavonoids can be recovered from the palm oil mill effluent (Wattanapenpaiboon and Wahlqvist, 2003).

The benefits of palm oil to health include reduction in the risk of arterial thrombosis and atherosclerosis (Van Jaarsvelds et al., 2002), inhibition of endogenous cholesterol biosynthesis, platelet aggregation, lowering of blood triglycerides (or reduced fat storage) as compared with polyunsaturated fat diets (Ong and Goh, 2002), retarding oxidation of low-density lipoproteins, promoting vascular relaxation (Abeywardena et al., 2002), and reduction in blood pressure. Lipolysis of palm-oil triacylglycerols containing oleic acid mainly at the sn-2 position and palmitic and stearic acids at sn 1 and 3 positions allows for the ready absorption of the 2-monoacylglycerols, while the saturated fatty acids are poorly absorbed (Ong and Goh, 2002). Unlike fresh palm oil, oxidized palm (resulting from processing for culinary purposes) induces an adverse lipid profile, reproductive toxicity, and toxicity of the kidney, lung, liver, and heart (Edem, 2002).

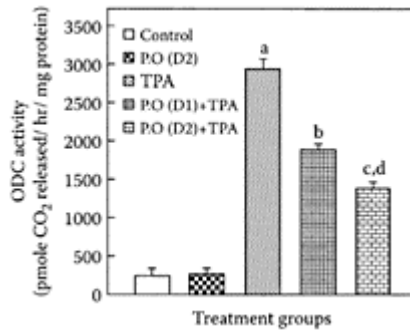


FIGURE P.72A Effect of pretreatment of palm oil on TPA-mediated epidermal ODC activity. Each value represents the mean DNA \pm SE of six animals, (a) Significantly different ($p<0.001$) compared with the acetone-treated control, (b) Significantly different ($p<0.01$) compared with the TPA-treated group, (c) Significantly different ($p<0.001$) compared with the TPA-treated group, (d) Significantly different ($p <0.01$) compared with the P.O. (D1)+TPA-treated group. P.O. (D1), significantly palm oil (100 L); P.O. (D2), palm oil (150 L). (From Kausar et al., *Cancer Lett.*, 192:151–160, 2003. With permission.)

Red palm oil is a rich source of β -carotene, α -carotene, and tocotrienols (Ong and Goh, 2002). Solomon (1998) showed that β -carotene in red palm oil can be used as a supplement to restore and preserve vitamin A in school children. Radhika et al. (2003) reported red-palmoil supplementation significantly improved maternal and neonatal vitamin A status and reduced the prevalence of maternal anemia. The effect of palm-oil carotene supplementation was shown by Nesaretman et al. (2002) to modulate the immune system by increasing peripheral blood NK cells and B-lymphocytes and suppress the growth of MCF-7 human breastcancer cells. The antitumor properties of palm oil (P.O.) were examined by Kausar et al. (2003) against 12-*O*-tetradecanoyl-phorbol-13 -acetate (TPA)-induced skin tumorigenesis in Swiss albino mice. The antiskin-tumor effects of palm oil (P.O.) involved inhibition of ornithine decarboxylase (ODC) and [(3)H]thymidine incorporation, conventionally used markers for

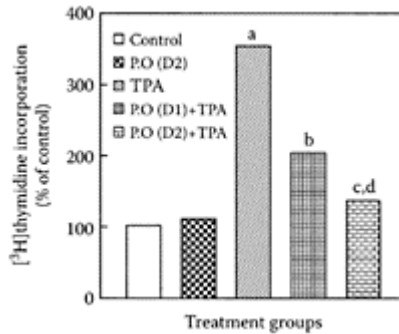


FIGURE P.72B Effect of pretreatment of palm oil on TPA-mediated [³H]thymidine incorporation in epidermal. The data represent the percentage of the acetone-treated control value. The actual acetone-treated control value is 5.00 ± 8.46 DPM/mg DNA. The TPA-treated control is 186 ± 9.66 DPM/mg DNA. The values represent the mean \pm six animals, (a) Significantly different ($p < 0.001$) compared with the acetone-treated control, (b) Different ($p < 0.05$) when compared with the TPA-treated group, (c) Significantly different ($p < 0.01$) compared with the TPA-treated group, (d) Significantly different ($p < 0.05$) when compared with the P.O.(D1)+TPA-treated group. P.O. (D1), palm oil (100 L); P.O. (D2), palm oil (150 L). (From Kausar et al., *Cancer Lett.*, 192:151–160, 2003. With permission.)

skin-tumor promotion and cutaneous oxidative stress (Figure P.72A, B).

Other studies showed the tocotrienol-rich fraction (TRF) of palm oil inhibited cell growth and induced apoptosis in both preneoplastic and neoplastic cells. Argawal et al. (2004) suggested that the mechanism of TRF-induced apoptosis in colon carcinoma cells was mediated by p53 signaling network independently of cellcycle association.

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Pau d'arco

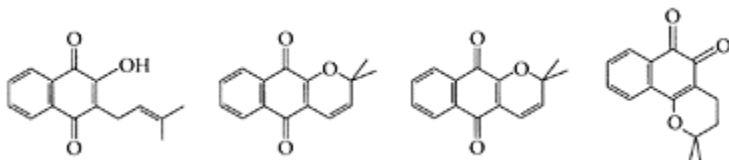
Tabebuia trees are native to the tropical rain forests in Central and South America. A commercial product, lapacho, obtained from its bark, is also known as Pau d'arco, Taheebo, and ipe-roxo. The main species used in folk medicine is *Tabebuia impetiginosa*. Pau d'arco has been used for many years as an anticancer, antifungal, antibacterial, and antiinflammatory drug (Zani et al., 1991). A number of naphthoquinones identified in *Tabebuia* included lapachol and dehydro- α -lapachol, together with α - and β -lapachones (Burnett and Thomson, 1967; Steinert et al., 1995).

Lapachol was reported to be effective against a number of tumors, as well as exhibited antiinflammatory activity (Subramanian et al., 1998; Almeida et al., 1990). The most extensively studied component in the heartwood of *T. impetiginosa* is β -lapachone, whose antitumor properties appear to involve the production of reactive-oxygen species

(Portela and Stoppani, 1996). In addition, β -lapachone has been found to induce apoptosis in tumor cells (Chau et al., 1998), as well as topoisomerase II-mediated DNA cleavage (Frydman et al., 1997). Further work by Muller et al. (1999) identified a number of lapacho compounds that were potent inhibitors of human keratinocyte growth of which naphtho[2,3-*b*]furan-4,9-diones were considered the most effective ingredients for treating psoriasis.

Anesini and Perez (1993) screened 132 extracts from Argentine folk-medicinal plants for antimicrobial activity using a penicillin-resistant strain of *Staphylococcus aureus*, *Escherichia coli*, and *Aspergillus niger*. Of these, *Tabebuia impetiginosa* produced some of the more active extracts against these organisms.

Koyama et al. (2000) isolated two cyclopentenone dialdehydes from the bark of *Tabebuia*. They were characterized as 2-formyl-5-(4'-methoxybenzoyloxy)-3-methyl-2-cyclopentene-1-acetaldehyde (1) and 2-formyl-5-(3',4'-dimethoxybenzoyloxy)-3-methyl-2-cyclopentene-1-acetaldehyde (2). Both compounds



Structure of lapacho compounds. (From Muller et al., *J. Nat. Prod.*, 62:1134–1136, 1999.)

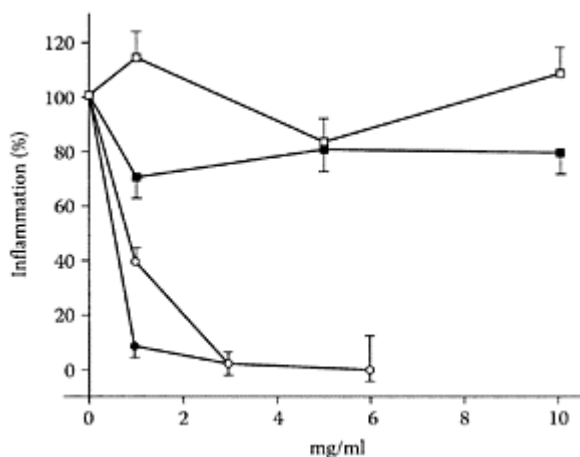


FIGURE P.73 Anti-inflammatory activities of 1 and 2 in the TPA-activated human PMN compared with alkylated benzoic acids, ○ 1; ● 2; □ 4-methoxybenzoic acid; ■ 3,4-

dimethoxybenzoic acid. (From
Koyama et al., *Phytochemistry*,
53:869–872, 2000. With permission.)

exhibited potent anti-inflammatory activity against 12-*O*-tetradecanoylphorbol (TPA)-activated human PMN compared to alkylated benzoic acids (Figure P.73).

The major volatile constituents of *T. impetiginosa* with antioxidant activity were shown by Park et al. (2003) to be 4-methoxybenzaldehyde, 4-methoxyphenol, 5-allyl-1,2,3-trimethoxybenzene (elimicin), 1-methoxy-4-(1E)-1-propenylbenzene (*trans*-anaethole), and 4-methoxybenzyl alcohol. These volatiles were found to be as effective as α -tocopherol and BHT in their ability to inhibit the formation of conjugated diene hydroperoxides from methyl linoleate and the oxidation of hexanal.

Warashina et al. (2004) recently reported the presence of 19 glycosides in the bark of *Tabebuia impetiginosa*. These included four iridoid glycosides, two lignan glycosides, two isocoumarin glycosides, three phenylethanoid glycosides, and eight phenolic glycosides.

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Pears

Pears are a good source of vitamin C (3.8 mg/100 g), vitamin K (4.5 mg/100 g), and dietary fiber (4 g/100 g). The average concentration of phenolic compounds in pears harvested at commercial maturity stage is 3.7 g/kg fresh pulp. The predominant phenolics are procyanidins (96 percent), together with hydroxycinnamic acids (2 percent), arbutin (0.8 percent), and catechins (0.7 percent). Sun-drying causes a decrease of 64 percent (on a dry-pulp basis) in the total amount of native phenolic compounds (Ferreira et al., 2002). A comparison of different pear cultivars showed a wide range in both phenolic content (272 to 475 mg of CtE/100 g fresh fruit) and *in vitro* antioxidant activity in the order of Forelle>Taylor>Peckham>Conference. A later study by Sanchez et al. (2003) compared six pear cultivars and found most of the phenolics were located in the peel, ranging from 1235 to 2005 mg/kg compared to 28–81 mg/kg for the corresponding flesh. Vitamin C was also higher in the peels, accounting for 116 to 228 mg/kg compared to 28–53 mg/kg in the flesh. A correlation of $r = 0.46$ was evident between antioxidant capacity and chlorogenic acid, with vitamin C only making a small contribution. Tanrioven and Eksi (2004) recently showed pear juice from seven different varieties ranged in total polyphenolics from 196 to 457 mg/L. Chlorogenic acid, the main phenolic, accounted for 73.1 to 249 mg/L, followed by epicatechin, which ranged from 11.9 to 81.3. The two remaining polyphenols were caffeic and p-coumaric acids, each accounting for 2.4–11.4 and 0.0–3.0 mg/L, respectively.

Leontowicz et al. (2002) examined the bioactive compounds in apples, peaches, and pears and their effect on lipids and antioxidant capacity in rats. Diets supplemented with apples and, to a lesser extent, with peaches and pears, improved lipid metabolism and plasma-antioxidant potential. They attributed the antioxidant properties of apples and pears to their polyphenols, phenolic acids, and flavonoids, with the peels being significantly higher ($p < 0.05$) than the pulp. Diets supplemented with fruit peels with added cholesterol exercised a significantly positive influence on rat plasma lipids, with pear peel being less effective than apple peel. The ability to counteract hypercholesterolemia and oxidative stress was consistent with a previous study using lyophilized apple by Aprikan et al. (2002). Because peels were much richer in polyphenols, the washed whole fruit was recommended.

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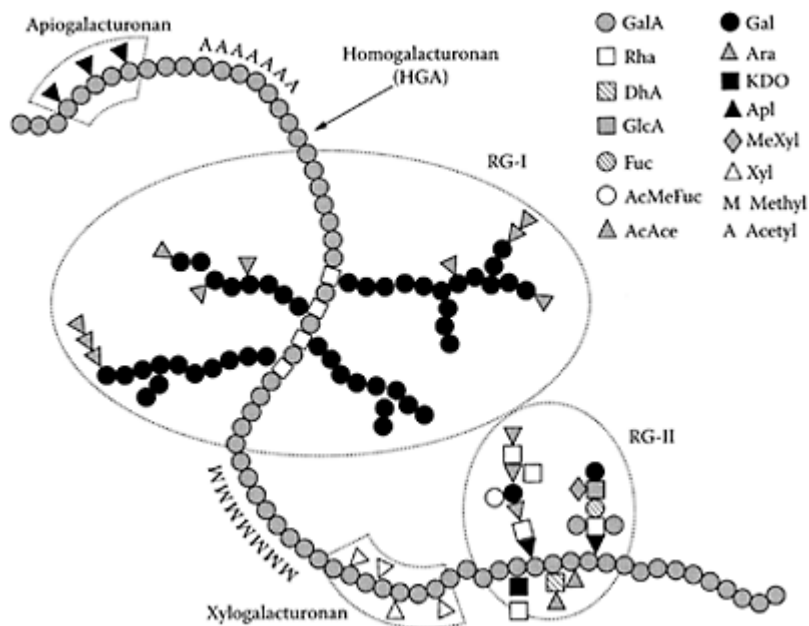
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Pectin

Pectin, the main component of primary plant cell walls of all land plants, encompasses a range of galacturonic acid-rich polysaccharides. Three major pectic poly saccharides, homogalacturonan (HGA), rhamnogalacturonan-I (RG-I), and rhamnogalacturonan-II (RG-II), are present in all primary cell walls, together with cellulose, hemicellulose, and protein (Perez et al., 2003). The “canonical” primary structure of pectins is depicted in Scheme P.42. Pectin is used extensively in the food, pharmaceuticals, and related industries. The importance of pectin is related to its ability to form a gel in the presence of Ca^{2+} ions or a solute at low pH (Thakur et al., 1997).

The quality of fibrin networks and the concentration of fibrinogen are both thought to contribute to increasing the risk of cardiovascular disease. Veldman et al. (1999) showed pectin influenced the fibrin-network architecture in hypercholesterolemic men without causing any changes in fibrinogen concentration. The beneficial effects of pectin appeared to be mediated by acetate as it is fermented in the gastrointestinal tract to acetate, propionate, and butyrate. Only acetate, however, reaches circulation in humans beyond the liver.

Vergara-Jimenez et al. (1999) demonstrated that pectin reversed hyperlipidemia associated with high-fat sucrose diets and had a potential antioxidant effect on circulating LDL. The protective effect of pectin on cardiovascular disease was shown by Park and coworkers (2000) to be due to an increase in fecal excretion of neutral sterols and hepatic microsomal fluidity. However, pectin increased risk factors for colon cancer by increasing the production of secondary bile acids and short-chain fatty acids in the colon. Rats fed low-molecular-weight pectin were found by Grizard et al. (2001) to significantly decrease triacylglycerols, total cholesterol,



SCHEME P.42 Schematic representation of the “canonical” primary structure of pectins. For the sake of simplicity, their schematic representations of HGA, RG-I, and RG-II are given, assuming that these three domains are covalently linked, although this point is not firmly established. (From Perez et al., *Biochimie*, 85:109–121, 2003. With permission.)

and insulin concentrations without changing postprandial blood-glucose levels.

Pectins also activate *in vitro* macrophages to be cytotoxic against tumor cells and microbial infections. Modifying citrus pectin, by enzymatic treatment to changes to the molecular structure of the long pectin chain, also inhibited metastases in animals with prostate cancer. Spontaneous lung metastases were also reduced by 60 percent if rats consumed 1 percent citrus pectin in their diets. Hayashi et al. (2000) reported that a pH-modified citrus pectin (MCP) significantly reduced the tumor size of colon-25 solid tumor implants in balb c mice. Rats receiving a low dose of (0.8 mg/mL) MCP produced a 38 percent ($p < 0.02$) decrease in tumor size compared to an impressive 70 percent ($p < 0.001$) reduction when animals were maintained on a high-dose (1.6 mg/mL) of MCP.

New developments with pectin-based formulations, particularly in the area of colon-specific drug-delivery systems, found that pectin showed great promise in engineering drugdelivery systems for oral drug delivery (Liu et al., 2003). Recent work by Liu et al. (2004) showed that composite matrices of pec-tin/poly(lactide-co-glycolide) had great potential for biomedical applications.

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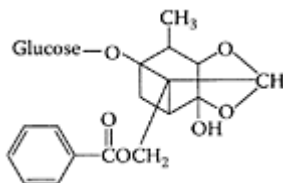
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Peony

Peonies, herbaceous cultivars of *Paeoniae alba* Radix (red peony root), the dried root of *Paeoniae lactiflora* Pallas or *Paeoniae veitchii* Lynch, originated in China more than 2,000 years ago. The root extract of peony was shown by Sakai et al. (1990) to inhibit the mutagenicity of benzo[a]pyrene-(B[a]p) metabolites. Tsuda et al. (1997) found one of the bioactives in peony root extract (*Paeoniae radix*), gallotannin, partially protected neuron damage in the hippocampus of 7-week-old Wistar rats induced by the cobalt focus epilepsy model, while paeoniflorin, a second bioactive, had no effect. However, when both bioactives were combined, they provided complete protection, similar to the whole peony-root extract. Treatment with paeoniflorin was shown by Tabata et al. (2000) to

reverse the suppressive effects of scopolamine and prenzepine (muscarinic receptor-antagonists) on long-term potentiation. Tabata et al. (2001) also found paeoniflorin ameliorated memory disruption mediated by the adenosine A1 receptor, which had a beneficial effect on learning and memory impairment in rodents.

The active principal of peony roots that lowered total and LDL cholesterol was identified by Shibata et al. (1963) as paeoniflorin. This water-soluble bioactive is pharmacologically active as an anti-inflammatory and antiallergic (Yamahara et al., 1982), antihyperglycemic (Hsu et al., 1997), and analgesic (Sugishita et al., 1984). More recent studies showed additional



Paeoniflorin. (From He et al., *J. Nat. Prod.*, 62:1134–1136, 1999. With permission.)

pharmacological effects, including antithrombosis (Ye et al., 2001), antihypotension (Cheng et al., 1999), and enhanced glucose uptake (Tang et al., 2003).

Yang et al. (2004) recently isolated paeoniflorin from the methanol extract of *Paeonia lactiflora* and examined its effect as an antihyperlipidemic agent. When 200 and 400 mg/kg of paeoniflorin were fed to experimentally induced hyperlipidemic adult male Wistar rats, plasma total-cholesterol levels were lowered significantly by 19.1 percent and 28.7 percent, respectively, in a dose-dependent manner. Under the same conditions, lovastatin, at a dose of 10 mg/kg, reduced plasma total cholesterol by 25.8 percent. Marked decreases in plasma triglycerides and LDL levels of 51.4 percent and 59.3 percent and 69.3 percent and 80.5 percent were also observed for the two doses of paeoniflorin, respectively. In contrast to lovastatin, which lowered HDL very slightly, paeoniflorin increased HDL by 14.9 percent and 6.3 percent for the two doses, respectively.

Chen et al. (1999, 2002) examined the pharmacokinetics of paeoniflorin in normal, healthy animals, while Ye and coworkers (2004) studied the effect of disease state on its pharmacokinetics. Using rats suffering from cerebral ischemia-reperfusion, they found marked differences in the pharmacokinetics of paeoniflorin between normal and diseased animals. For example, elimination of paeoniflorin slowed down in the ischemic-reperfusion rats, pointing to its accumulation in the pathological state. This information will ensure greater safety and efficacy when using paeoniflorin in clinical applications.

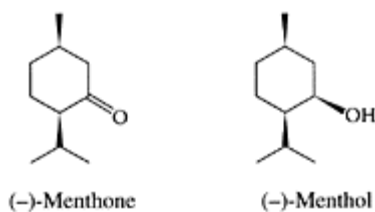
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Peppermint (*Mentha piperita*)

Peppermint is a very popular herb with a unique flavor. The oil from peppermint is currently used in cosmetic formulations as a fragrance component. Both peppermint and peppermint oil have psychoactive properties and are believed to be effective for treating nervous disorders and mental fatigue (Tisserand, 1993). The oil is composed primarily of menthol and menthone. Other possible constituents include pulegone, menthofuran, and limone. Because of the toxicity of pulegone, this constituent is limited to



Adapted from Hall, *Eur. J. Pharmacol.*, 506:9–16, 2004.

< or=1 percent (Nair et al., 2001). Other microelements and macroelements measured in peppermint were As, Cd, Cu, Fe, Mg, Pb, and Zn (Fijalek et al., 2003). Peppermints also contain antioxidants (i.e., >75 mmol/100 g) (Dragland et al., 2003). They are usually taken after a meal because of their ability to reduce indigestion and colonic spasms by reducing the gastrocolic reflex. It was recently shown that peppermint has a potential role in the management of certain procedures, such as colonoscopy (Spirling and Daniels, 2001) and during upper endoscopy (Hiki et al., 2003). The oil is harmless and acts locally in the stomach and duodenum to produce smooth-muscle relaxation in healthy volunteers (Micklefield et al., 2003).

May and coworkers (2003) demonstrated good tolerability and a favorable risk-benefit ratio of a fixed combination of 90 mg peppermint oil and 50 mg caraway oil for the treatment of functional dyspepsia. Pittler and Ernst (1998) reviewed clinical trials using peppermint extracts and were unable to establish beyond a reasonable doubt the efficacy of peppermint as a symptomatic treatment for irritable bowel syndrome.

A recent study by Norrish and Dwyer (2005) showed peppermint diminished daytime sleepiness, normally associated with sitting in a dark room. The invigorating effects of peppermint oil could enable people to remain awake, such as during the night shift.

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Peppers

see also Capsaicin, Chili peppers, and Red peppers Peppers (*Capsicum annum* L.) are good sources of provitamin carotenoids, α -carotene, β -carotene, and cryptoxanthin and a wide array of neutral and acidic phenolic compounds. As peppers mature, the concentrations of these carotenoids increase, together with phenolic acids, capxanthin, and zeaxanthin (Howard et al., 2000). Lutein, on the other was shown to decline. Peppers contain high levels of L-ascorbic acid and carotenoids at maturity, contributing 124–338 percent of the RDA for vitamin C and 0.33–336 RE/100 g provitamin A carotenoids. Peppers also contain oxygenated carotenoids or xanthophylls, which do not possess vitamin A activity but are still effective free-radical scavengers and may help to prevent age-related macular degeneration and cataracts.

Jimenez et al. (2003) reported that antioxidant capacity and ascorbate content were higher in red peppers than green peppers and that storage increased ascorbate content in both green and red fruits.

The concentration of capsaicinoids in fresh peppers was variable, depending on the relative pungency of the pepper type and geographical origin of the pepper (Reilly et al., 2001). The health-related properties are discussed under capsaicin. Fresh, whole, homogenized peppers have characteristic volatile components, including hydrocarbons, terpenes, alcohols, phenols, ethers, aldehydes, ketones, esters, pyrroles, pyrazines, and sulfurous compounds (Oruna-Concha et al., 1998).

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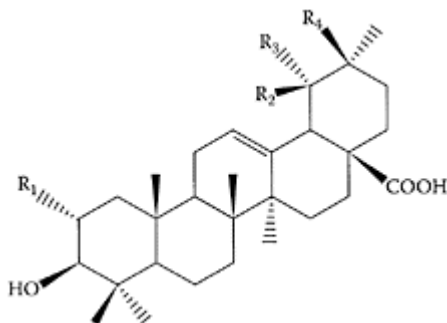
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Peptides

see **Biopeptides**

Perilla

Perilla (*Perrilla frutescens* L.), a common annual weed in the Eastern United States, is a commercial crop in Asia. It is a member of the mint family, and its leaves are used for medicinal purposes. Asian herbalists prescribe perilla for cough and lung afflictions, influenza prevention, etc. Volatile components in perilla oil include an aldehyde chemotype that is the basis of Japanese Ao-shiso, a medicine with an agreeable fragrance (Koezuka et al., 1986). In addition, a perilla ketone was shown to be a very effective laxative without causing diarrhea in laboratory mice (Koezuka et al., 1985). The leaves of perilla have been used for centuries in Chinese medicine for treating a variety of diseases. Chen and coworkers (2003) identified three bioactive triterpenes in perilla leaves as tormentic acid (TA), oleanolic acid (OA), and ursolic acid (UA).



Structure of perilla leaf bioactive triterpenes. (From Chen et al., *J. Pharm. Biomed. Anal.*, 32:1175–1179, 2003. With permission.)

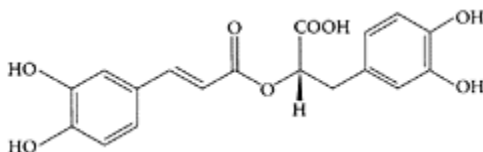
TA: R₁=R₃=OH, R₂=CH₃, R₄=H

OA: R₁=R₂=R₃=H, R₄=CH₃

UA: R₁=R₃=R₄=H, R₂=CH₃

The major poly phenol in perilla-leaf extract, rosmarinic acid, was shown by Osakabe et al. (2002) to reduce liver damage induced by lipopolysaccharides and D-galactosamine by scavenging or reducing the activities of super-oxide or peroxynitrite.

Perilla-seed oil is used extensively for cooking in Asian countries. It is one of the richest sources of alpha linolenic acid, reported to prevent atherosclerosis and chemically induced cancer, as well as improves immune and mental function (Yamamoto et al., 1987; Shoda et al., 1995; Sadi et al, 1996; Onogi et al., 1996). The hypolipidemic effect of perilla oil was recently demonstrated by Kim et al. (2004), who showed that feeding rats a diet rich in perilla oil suppressed hepatic fatty-acid synthase, which significantly lowered plasma triacylglycerol levels.



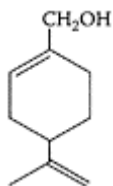
Rosmarinic acid. (From Osakabe et al., *Free Rad. Biol. Med.*, 33:798–806, 2002. With permission.)

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Perillyl alcohol and Perillaldehyde

Perillyl alcohol is a naturally occurring monoterpene in citrus fruits, herbs, and spices with anticancer properties (Gould, 1995). Several animal-tumor models reported the anticancer action of perillyl alcohol in breast, liver, colon, and prostate cancer (Haag and Gould, 1994; Mills et al., 1995; Kelloff et al., 1996). Samouti et al. (1999) found



Perillyl alcohol. (Adapted from Zhang et al., *J. Chromatogr. B.*, 728:85–98, 1999).

perillyl alcohol induced transient expression of the *c-jun* and *c-fos* genes, as well as phosphorylation of *c-jun* protein-cultured breast-cancer cell. Both events are associated with activation of an activator protein (AP)-1-dependent reporter gene. These changes are associated with perillyl alcohol's ability to induce apoptosis, or cell death. Phase I human clinical trials with perillyl alcohol indicated it is a relatively nontoxic compound for treating certain human tumors (Hudes et al., 2000; Ripple et al., 2000). Bardon and coworkers (2002) established the molecular mechanisms of perillyl alcohol and its major metabolite, perillic acid (PA), as antiproliferative agents using human colon-cancer cells. These monoterpenes arrested the growth of cancer cells by increasing the expression of the cdk inhibitor p21^{Waf1/Cip1} and decreasing the expression of cyclin D1 and its partner, cdk4. The effect of perillyl alcohol on two human lung-cancer cell lines, H383, nonsmall cell lung cancer cells derived from adenocarcinoma and H322, bronchioloalveolar carcinoma cells, was reported recently by Xu and coworkers (2004). Perillyl alcohol stimulated or sensitized lungtumor cells to apoptosis via activation of caspase-3, a key executioner of apoptosis. This is evident in Figure P.74 where the highest dose of perillyl alcohol (1.5 mM) significantly decreased cell proliferation in H322 and H838 cells by 83% and 70%, respectively. The increased sensitivity of perillyl-alcohol-treated cells suggested it could be combined with other drugs to maximize chemotherapeutic effects. Ahn et al. (2003) showed the anticancer properties of perillyl alcohol on SCK mammary carcinoma cells of female A/J mice was significantly enhanced by hypothermia. The latter is used for treating certain human tumors, so that the synergism observed in this study could lead to a combination of perillyl alcohol and hyperthermia.

In vitro studies with human carcinoma cell lines (BroTo and A5459) by Elgebde and coworkers (2003) found perillaldehyde only weakly induced apoptosis compared to perillyl alcohol, which probably involved a different mechanism.

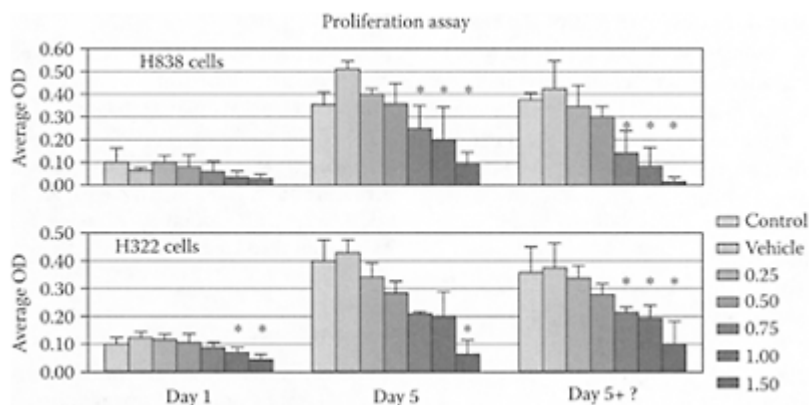


FIGURE P.74 Perillyl alcohol inhibition of cell proliferation. H322 and H838 cells were treated with either 0.06% ethanol (vehicle controls) or perillyl alcohol at concentrations ranging from 0.25 to 1.5 mM for 1 and 5 days. Untreated cells served as an additional negative control. The sulforhodamine B (SRB) cell proliferation assay was performed. The individual bars represent the mean values \pm standard deviation of three individual experiments performed in triplicate. Asterisks (*) indicate values that are statistically significant at a minimal of $p < 0.05$ relative to vehicle control (Xu, *Toxicol. Applied Pharmacol.*, 195:232–246, 2004).

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Persimmon

Persimmon (*Diospyros khaki*) is grown in Asia, where the leaves are brewed into a tea for its health benefits, such as homeostasis, diuretic, constipation, and hypotension. These properties reflect the health-promoting effects of flavonoids, such as kaempferol, and the higher total, soluble, and insoluble dietary fibers, total phenols, epicatechin, gallic, and p-coumaric acids, as well as minerals Na, K, Mg, Ca, Fe, and Mn compared to apples (Gorinstein et al., 2001).

In vitro and *in vivo* studies with persimmon and grape extracts by Ahn et al. (2002) showed both were potent antioxidants. Using DPPH, both extracts exhibited similar free-radical-scavenging activities of around 87–88 percent, which was attributed to their high tannin contents. *In vivo* studies with Sprague-Dawley rats resulted in a significant inhibition of lipid peroxidation. However, Figure P.75 shows that the persimmon extract was more effective in lowering hepatic TBARS, secondary oxidation products, than the grape-seed extract. In addition, there was a corresponding reduction in hepatic lipid-peroxide levels accompanied by an increase in catalase and superoxide dismutase (SOD) levels.

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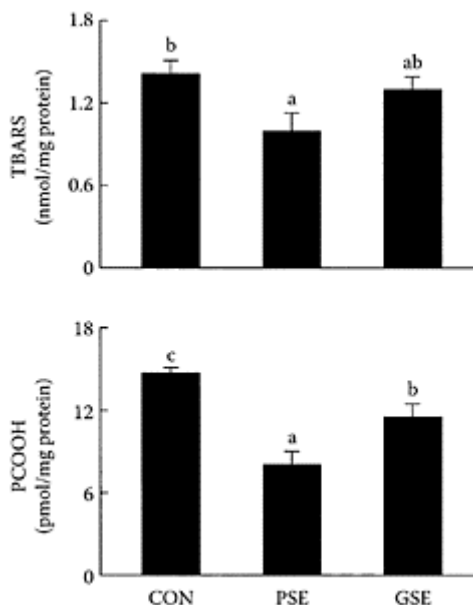


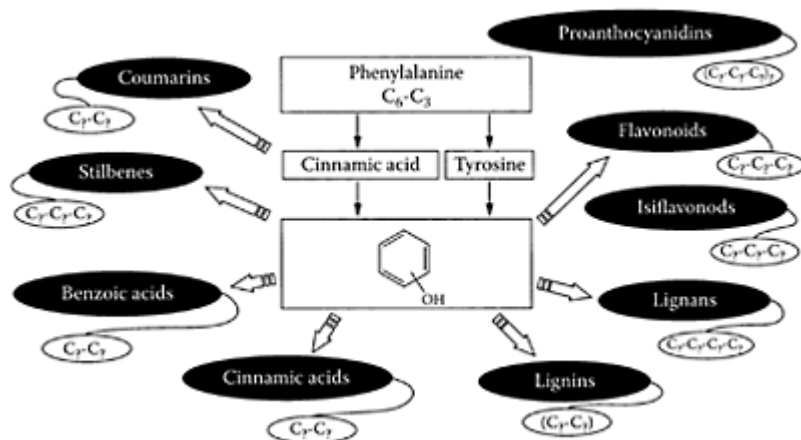
FIGURE P.75 Effects of PSE compared to GSE on the amount of thiobarbituric-acid reactive substances (TBARS; top panel) and phosphatidylcholine hydroperoxide (PCOOH; bottom panel) in the liver of rats. Each bar represents the means \pm SEM of five rats. Mean values with different superscripts are significantly different ($P < 0.05$). CON, control; PSE, persimmon seed extract; GSE, grape-seed extract. (From Ahn et al., *Nutr. Res.*, 22:1265–1273, 2002. With permission.)

Phenols

see also Flavonoids Phenols and polyphenols are ubiquitous in plant foods and, depending on their bioavailability, may play an important role as antioxidants. A number of comprehensive reviews on the health aspects of polyphenols are recommended to the reader (Mahmoud et al., 2000; Zheng and Ramirez, 2000; Parr and Bolwell, 2000; Hollman, 2001). A large variety of plant phenols are synthesized via phenylpropanoid pathways, as shown in Scheme P.43. One of these, the flavonoids, consists of six different classes that account for more than 4,000 different compounds (see Flavonoids). The overall beneficial activities of phenols and polyphenols include their potent antioxidant activity, preventing oxidative damage to DNA, lipids, and proteins associated with prevention of chronic diseases. The inverse association between flavonol intake and cardiovascular disease points to their preventive role in atherosclerosis. The bioavailability of flavonoids in humans is only around 1 percent, and recent work by Lotito and Frei (2004) suggested that the increased plasma antioxidant capacity recorded in humans following apple consumption may not be due to apple-derived flavonoids but to the effect of fructose on urate.

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SCHEME P.43 Most plant phenols are synthesized via the phenylpropanoid pathway and share a common building block, the C₆-C₃ unit. (From Hollman, *J. Sci. Food Agric.*, 81:842–852, 2001. With permission.)

ment of the diet by modifying the phenols content or profile, *J. Sci. Food Agric.*, 80:985–1012, 2000.

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2-Phenylethyl isothiocyanate (PEITC)

2-Phenylethyl isothiocyanate (PEITC) is formed in some *Brassica* species, such as watercress, by the action of myrosinase on its precursor gluconasturtiin (2-phenylethyl glucosinolate) (Scheme P.44). This occurs by chewing or in food preparation. PEITC is recognized as one of the most effective anticancer agents (Huang et al., 1998) by inhibiting phase I enzymes and activating phase II enzymes (Hecht et al., 1999). In addition, *in vitro* and *in vivo* studies showed PEITC had therapeutic value by inducing apoptosis in cells resistant to chemotherapy due to mutation of p53 (Huang et al., 1998; Xiao and Singh, 2002; Yang et al., 2002). Hu and coworkers (2003) reported induction of apoptosis in human HT-29 colon adenocarcinoma cells by PEITC was both time-dependent and dose-dependent, mediated via the mitochondrial caspase cascade, with

activation of the mitogen-activated kinase JNK critical for initiation of the process. Using isolated hepatocyte mitochondria from rat hepatoma HepG2 cells, Rose et al. (2005) showed that decreased cell viability by PEITC was concentration dependent with an IC_{50} of 20 mM (Figure P.76). The inability of pharmacological inhibitors of mitochondrial permeability, cyclosporine A, trifluoperazine, and Bongkreikic acid, to prevent PEITC-induced apoptosis of HepG2 cells suggested the key target was the mitochondria. Apoptosis of HeG2 cells by PEITC appeared to be via the pore-forming ability of proapoptotic Bax.



SCHEME P.44 Generation of the phenylethyl isothiocyanate (PEITC) from gluconasturtiin (GNST) by myrosinase (MYR) action. (From Canistro et al., *Mutat. Res.*, 545:23–35, 2004. With permission.)

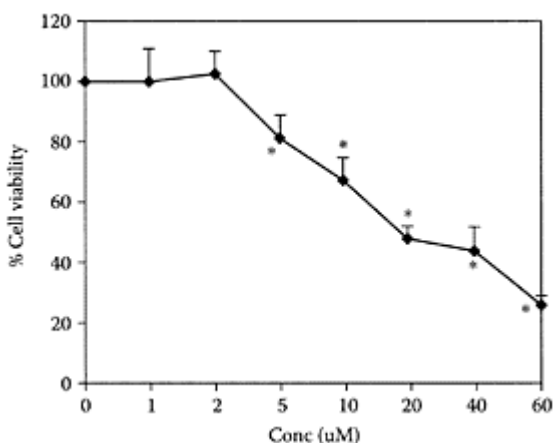


FIGURE P.76 Concentration-dependant effects of PEITC on HepG2 cells as determined at 24 h using the crystal violet viability assay. Data are representative of three separate experiments (means \pm SD). (From Rose

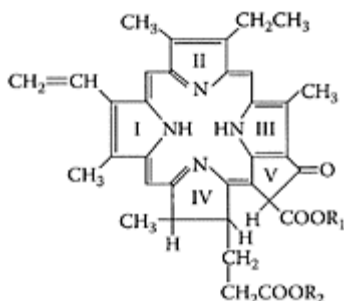
et al., *Int. J. Biochem. Cell Biol.*, 37:100–119, 2005. With permission.)

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Pheophytin and Pheophorbide

see also Chlorophyll and Chlorophyllin The methanol extracts from eight Japanese edible seaweeds were found to suppress genotoxin-induced *umu C* gene expression in *Salmonella typhimurium*. The edible seaweeds with strong antigenotoxic properties were *Porphyra tenera* and *Enteromorpha prolifera* (Okai et al., 1994). The bioactives identified in *P. tenera* extracts were β -carotene, lutein, and chlorophyll *a* (Okai et al., 1996). Further work by Okai and Higashi-Okai (1997a) showed pheophytin *a*, a degradation product of chlorophyll *a*, was responsible for these suppressor effects. Pheophytin *a* and *b* were also identified as potent as antigenotoxic compounds in the nonpolyphenolic fraction of green tea, capable of suppressing the *umu C* gene (Okai and Higashi-Okai, 1997b). Subsequent work by Higashi-Okai et al. (1998) reported the antitumor suppressors in the nonphenolic fraction from green tea. Using a *Salmonella typhimurium* strain TA100, Chernomorsky and coworkers (1999) found the antimutagenic properties of chlorophyll derivatives, pheophytin, pyropheophytin, and pheophorbide,



Structure of chlorophyll derivatives. (From Chernomorsky et al., *Teratogenesis Carcinogen. Mutagen.*, 19:313–322, 1999. With permission.)

Pheophytin *a*; $R_1 = \text{CH}_3$, $R_2 = \text{C}_{20}\text{H}_{39}$

Pyropheophytin *a*; $R_1 = \text{H}$; $R_2 = \text{C}_{20}\text{H}_{39}$

Pheophorbide *a*; $R_1 = \text{CH}_3$; $R_2 = \text{H}$

against the indirect-acting mutagen 3-methyl-cholanthrene, showed a similar dose-response pattern (Figure P.77). However, in the presence of the direct-acting mutagen, *N'*-nitro-*N'*-nitrosoguanidine, derivatives acted quite differently, with the phytol-containing derivatives (pheophytin and pyropheophytin) being far more effective than pheophorbide, which lacked the phytol group. Thus, food sources containing these chlorophyll derivatives may have a role in cancer prevention.

Using yeast cells (*Saccharomyces cerevisiae*), Okai and Higashi-Okai (2001) reported that chlorophyll *a* and pheophytin *a* from green tea were both more effective than chlorophyllin in preventing the endocrine disrupter, p-nonylphenol, from suppressing cell growth and cellular respiration. The antioxidant properties of chlorophyll *a* and pheophytin *a* reported previously by Endo et al. (1985) and Higashi-Okai et al. (2000), could explain, in part, the mechanism involved, as well as their ability to adsorb or bind p-nonylphenol.

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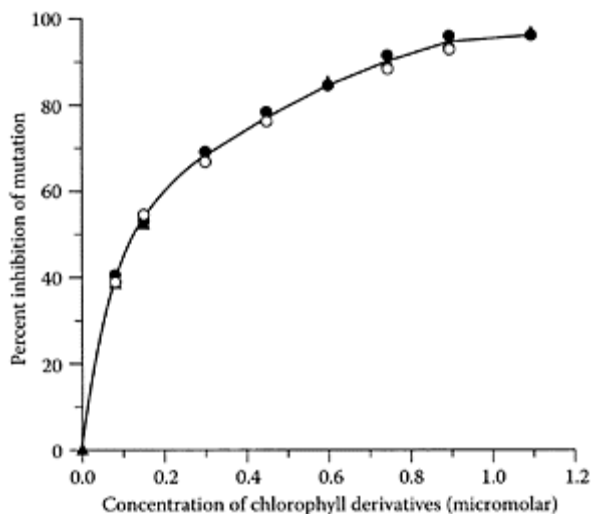
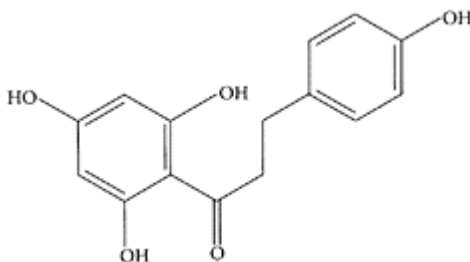


FIGURE P.77 Antimutagenic activity of pheophytin *a* (●), pyropheophytin *a* (▲), and pheophorbide *a* (○) against 3-methylcholanthrene. (From Chernomorsky et al., *Teratogenesis Carcinogen. Mutagen.*, 19:313–322, 1999. With permission.)

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Phloretin

see also Phloridzin Phloretin, a polyphenolic compound found in the root bark of apple trees, is the aglycone of phloridzin. It was recently found to enhance skin permeation of a number of drugs (Valenta et al., 2001; Valenta and Nowak, 2001; Auner et al., 2003a, b). Research by Curtis-Prior et al. (1980) showed that phloretin derivatives were antagonists of prostaglandins, which pointed to their therapeutic potential as anti-inflammatory agents. Auner and Valenta (2004) confirmed the ability of phloretin to increase lidocaine skin permeation. The effect of lidocaine, a local anesthetic used to suppress burning, itching, surgical operations, injections, and dermatological



Phloretin. (From Valenta et al., *Eur. J. Pharmaceut. Biopharmaceut.*, 57:329–336, 2004. With permission.)

diseases, was enhanced 1.39-fold in a hydrophilic formulation and 1.25 and 1.76 in lipophilic formulations.

Valenta and coworkers (2004) studied the mechanism of phloretin and 6-ketocholestanol interaction with the lipid layer which decreased the lipid phase transition temperature of 1,2dimyristyl-*sn*-3-phosphocholine (DMPC) and 1,2-palmitoyl-*sn*-glycero-3-phosphocholine (DPPC) liposomes, resulting in a higher fluidity of the membrane. Phloretin modified the binding and translocation rates of hydrophobic ions in lipid-vesicle systems, resulting in lowering and raising of the internal dipole potential (Franklin and Cafiso, 1993).

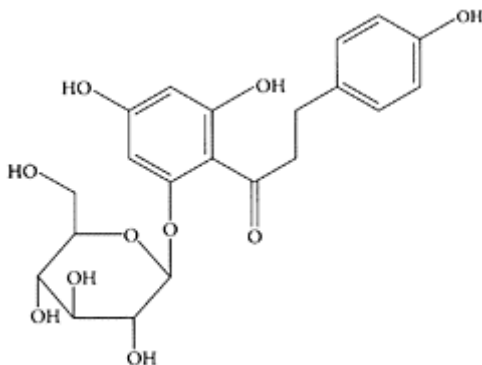
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Phloridzin

see also Apples and Phloretin Phloridzin, a poly phenol found in apples, has been used to inhibit the intestinal Na⁺/glucose transporter (SGLT1) (Hirayama et al., 1998). Mizuma and Awazu (1998) reported phloridzin was metabolized to its aglycone, phloretin, with both inhibiting glucuronidation of p-nitrophenol, acetaminophen, and 1-naphthol in rats. Inhibition of glucuronidation metabolism improves the intestinal absorption of those drugs susceptible to glucuronidation. A recent study by Andlauer and coworkers (2004) found phloridzin amplified the absorption of the isoflavone, genistin, 2.5-fold. Isoflavones are generally poorly absorbed so that a high intake is normally required to ensure their chemoprevention effects. A combination of nutraceuticals, such as genistin, with functional phloridzin-



Phloridzin. (From Valenta et al., *Eur. J. Pharmaceut. Biopharmaceut.*, 57:329–336, 2004.)

containing foods provides a novel way of enhancing genistin absorption and increasing its efficacy in cancer prevention.

The antioxidant and radical-scavenging activities of polyphenols, including phloridzin and 3-hydroxy-phloridzin, was reported in apple pomace, the waste product produced in the processing of apple juice. The health-protecting properties of apples may be attributed to these compounds, as Hertog and coworkers (1993) provided data that suggested that men who ate 110 g of apple or day had a 49 percent lower risk factor for heart attack compared to those eating much less (18 g).

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Phosphatides

see also Phosphatidylcholine and Phosphatidylserine These include numerous lipids in which phosphoric acid, as well as fatty acids, are esterified to glycerol and are found in all living cells and in bilayers of plasma membranes. Phospholipids have been associated with a number of health benefits. A glycerol-free phospholipid analogue, hexadecylphosphocholine (HePC), was shown by Wieder et al. (1996) to exhibit antitumor properties using cultured human breast fibroblasts. The antitumor activity appeared to be related to activation of cellular phospholipase D.

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Phosphatidylcholine

Phosphatidylcholine (PC), or lecithin, constitutes a major portion of cellular phospholipids and displays unique molecular species in different cell types and tissues. PC is also the major delivery form of the essential nutrient choline and is involved in the hepatic form, which is involved in the hepatic export of very-low-density lipoproteins. The main roles of PC are the flow of information within cells from DNA to RNA to proteins and the formation of cellular energy and intracellular communication or signal transduction. PC also has a marked fluidizing effect on cellular membranes. Decreased cell-membrane fluidization and breakdown of cell-membrane integrity, as well as impairment of cell-membrane repair mechanisms, are associated with a number of disorders, including liver disease, neurological diseases, various cancers, and cell death.

Many agents that perturb PC homeostasis also induce cell death, but the signaling pathways that mediate this cell death have not been well defined (Cui and Houweling, 2002). PC is absorbed into the mucosal cells of the small intestine, mainly in the duodenum and upper jejunum, following some digestion by the pancreatic enzyme phospholipase, producing lysophosphatidylcholine, which is transported by the lymphatics in the form of chylomicrons to the blood. PC is transported in the blood in various lipoprotein particles, including very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), and is then distributed to various tissues in the body. Some PC is incorporated into cell membranes and some is metabolized to choline, fatty acids, and glycerol.

PC may have a beneficial effect by restoring liver function in a number of disorders (Hatashi et al., 1999), including alcoholic fibrosis and possibly viral hepatitis (Canty and Zeisel, 1994). Dietary lecithin (a complex mixture of phospholipids and other lipids) has been used in emergencies and in the treatment of atheroma plaques in cardiac diseases. It promotes a return to normal of the plasma lipoprotein-distribution profile and the removal of lipid from established atherosclerotic plaques in Dutch-Belted rabbits (Hunt and Duncan, 1985). Recently, PC was used to treat localized fat deposits, such as lower eyelid fat pads (Hexsel et al., 2003; Ablon and Rotunda, 2004).

Some studies found PC had a positive effect on memory (Ladd et al., 1993; Chung et al., 1995). Masuda and coworkers (1998) found egg PC, together with vitamin B₁₂, improved memory impairment of rats with nucleus basalis Magnocellularis (NBM) lesions. PC has also been used to treat manic conditions (Cohen et al., 1982) and in some tardive dyskinesia (Gelenberg et al., 1989). PC has even been evaluated in Parkinson's disease (Tweedy and Garcia, 1982). Cytidine 5'-diphosphocholine, an essential intermediate in the biosynthetic pathway of PC, was reported to be effective as cotherapy for Parkinson's disease (Secades and Frontera, 1995) and was recently shown to have a positive effect on memory, with demonstrated hippocampal morphology resembling that of younger animals (Crespo et al., 2004). There is some inconclusive evidence that PC may be useful in managing Alzheimer's disease and some cognitive disorders (Higgins and Flicker, 2003; McDaniel et al., 2003).

A possible future role for PC suggested by Gallo et al. (2003) is in cancer therapy. A complex of silybin/phosphatidylcholine (IdB 1016) appeared to have clinical potential in the management of recurrent ovarian cancer.

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Phosphatidylserine

Phosphatidylserine (PS), a natural component of the brain cortex, is the major phospholipid in the outer surface of brain-synaptic membranes. It plays an important role

in signal transduction, secretory-vesicle release, and cell-to-cell communication (Nishizuka, 1984; Blokland et al., 1999). PS may be the signal by which apoptotic cells are recognized and phagocytosed (Brauer, 2003). Studies with geriatric patients suffering from Alzheimer's or Parkinson's disease or arteriosclerotic encephalopathy suggested that prolonged treatment with PS particularly improved attention, memory, withdrawal and apathy, sleep disturbances, and mood (Maggioni et al., 1990). A significant improvement in depressive symptomatology in patients with major depressive disorders was found in subsequent studies, also with PS administration compared to controls (Brambilla et al., 1996; Brambilla and Maggioni, 1998). Crook et al. (1991) treated patients with age-associated memory impairment with a daily dose of PS (100 mg/day tid) over 12 weeks and found improved performance tests related to learning and memory tasks of daily life compared to those receiving the placebo. Castilho et al. (2004) found PS exerted an antidepressive effect in rats using the forced swimming test but did not act as a cognitive enhancer, as it was ineffective in the watermaze test.

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Phospholipids

see Phosphatides, Phosphatidyl choline, and Phosphatidylserine

Phosvitin Phosvitin, a phosphoprotein known as an iron-carrier in egg yolk, binds almost all of the yolk iron. The formation of phosvitin-Fe complex promotes the precipitation of Fe in the small-intestinal tract, which may be responsible for the poor

iron availability of egg and egg yolk (Sato et al., 1984). Ishakawa et al. (2004) reported that phosvitin acts as a natural antioxidant by chelating iron ions. It accelerates Fe(II) autoxidation and thus decreases the availability of Fe(III) for participation in the OH-generating Fenton reaction. These results provide insight into the mechanism of protection of the developing embryo against iron-dependent oxidative damage. Phosvitin was found to be more effective in cooked ground pork compared with uncooked, salted ground pork (Lee et al., 2002). Kobayashi et al. (2004) demonstrated that the role of phosvitin in bone formation was to enhance nucleation of hydroxyapatite crystals on collagen in the same way as that observed in human bone.

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Phyllanthus

Plants of the genus *Phyllanthus* (family Euphorbiaceae) are found in most tropical and subtropical countries. They have been used in folk medicine to treat kidney and urinary bladder disturbances, intestinal infections, diabetes, and hepatitis B. Studies conducted on extracts and purified compounds from these plants by Calixto and coworkers (1998) confirmed their

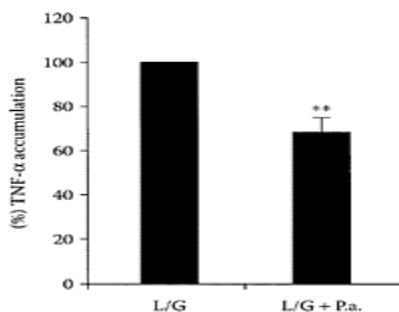


FIGURE P.78 *In vivo* inhibition of TNF- α production by *P. amarus*

extract (P.a.). Male BalbA2 mice received either 45 mg/kg *Phyllanthus* extract or saline/DMSO i.p. 30 min later, mice were injected with 500 mg/kg galactosamine i.p., and immediately afterwards with 1.5 mg/kg of LPS(L/G). After 90 min, a serum sample was obtained by tail bleeding and murine TNF- α was determined by ELISA. Three independent experiments were carried out with four animals each. TNF- α level of the respective control group was normalized to 100 percent. Data are expressed as means \pm SEM. ** $p < 0.01$ represents statistical differences from animals treated with LPS/galactosamine only. (From Kiemer et al., *J. Hepatol.*, 38:289–297, 2003. With permission.)

efficacy as an antiviral, as well as in the treatment of genitourinary disorders, and as antinociceptive agents. They also found that *Phyllanthus* had potential therapeutic benefits in the management of hepatitis *B. nefrolitase* and in painful disorders. The leaves of *Phyllanthus* were shown earlier by Ihantola-Vormisto et al. (1997) to exert inhibitory activity on human polymorphonuclear leukocytes and antipyretic and platelets, which confirmed their antiinflammatory and antipyretic properties for use in traditional medicine. The anti-inflammatory properties of standardized *Phyllanthus* extracts were demonstrated by Kiemer and coworkers (2003) by their ability to inhibit induction of endotoxin-induced nitric-oxide synthase (iNOS), cyclooxygenase (COX-2), and TNF- α production in rat Kupffer cells, in RAW264.7 macrophages, and in human whole blood. The significant inhibition of TNF- α in Male BalbA2 mice in the presence of the *Phyllanthus* extract is shown in Figure P.78.

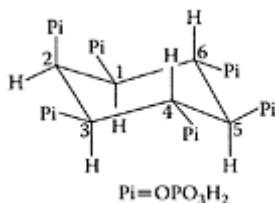
Huang et al. (2004) recently demonstrated the anticancer properties of *Phyllanthus urinaria* on human myeloid leukemia (HL-60) cells, which appeared to be mediated via a ceramide-related pathway. An increase in the inhibition of HIV-1 reverse transcriptase was reported by Wagner and Notka (2002) to be linear, with increasing concentrations of gallotannins extracted from *Phyllanthus*, suggesting its potential for preventing and treating retrovirus-related diseases, such as human immunodeficiency virus (HIV).

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Phytic acid

Phytic acid (*myo*-inositol hexaphosphate, IP₆) is the major storage form of phosphorus and accounts for 1–5 percent by weight of edible legumes, cereals, and oilseeds (Graf and Eaton, 1995). Historically, phytic acid was considered to be an antinutrient because of its ability to bind divalent cations,



Structure of phytic acid. (From Chen and Li, *J. Chromatogr. A.*, 1018:41–52, 2003. With permission.)

such as calcium, magnesium, zinc, and iron, reducing their bioavailability (Reddy et al., 1989). However, it has since been recognized as an antioxidant because of its potent inhibition of iron-catalyzed hydroxyl-radical formation (Rimbach and Pallauf, 1998). In addition, phytic acid has also been shown to have anticarcinogenic (Shamsuddin et al., 1996), as well as hypoglycemic and hypolipidemic, (Rickard and Thompson, 1997) properties.

Obata (2003) examined the effect of phytic acid on the neurotoxin 1-methyl-4-phenylpyridinium (MPP⁺), a potent Parkinson-causing reagent formed in the brain from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Phytic acid suppressed the ability

of this neurotoxin to induce hydroxyl-radical generation by chelating the required iron, suggesting its clinical potential as an antioxidant.

Phytic acid was shown earlier by Midorikawa et al. (2001) to prevent the formation of reactive-oxygen species, such as 8-oxodG, in cultured cells treated with an H_2O_2 -generating system. The dramatic reduction in the formation of oxidative DNA damage in the presence of phytic acid is evident from Figure P.79 compared to the inability of *myo*-inositol

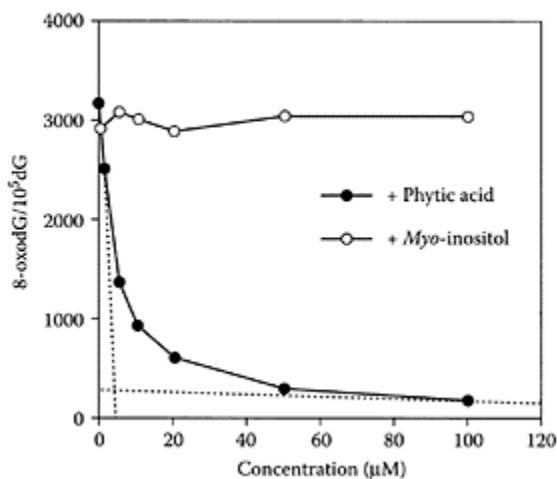


FIGURE P.79 Formation of 8-oxodG in calf thymus DNA induced by H_2O_2 and Cu(II) in the presence of phytic acid or *myo*-inositol. Calf thymus DNA fragments (100 μM/base) were incubated with 20 μM CuCl_2 , 100 μM H_2O_2 , and indicated concentrations of phytic acid (closed circles) or *myo*-inositol (open circles) at 37°C for 15 min. After ethanol precipitation, the DNA was digested into nucleosides with nuclease P1 and calf-intestine phosphatase and analyzed with an HPLC-ECD system. Intersection of dotted lines showed the concentration of phytic acid to inhibit 8-oxodG formation. (From Midorikawa et al.,

to inhibit 8-oxodG formation. The antioxidant properties of phytic acid were due to its ability to chelate transition metal ions. The possible role of phytic acid in cancer prevention was further confirmed by Muraoka and Miura (2004), who showed that phytic acid, and not *myo*-inositol, inhibited xanthine oxidase, the enzymatic source of superoxide (O_2^-). In addition, phytic acid also prevented the formation of ADP-iron-oxygen complexes. The potential of phytic acid to prevent the formation of oxygen radicals in the intestine could prevent the development of chronic diseases, such as cancer.

A systematic review of phytic acid as a novel broad-spectrum, antineoplastic agent by Fox and Eberl (2002) suggested its role in cancer prevention warranted phase I and phase II human clinical trials.

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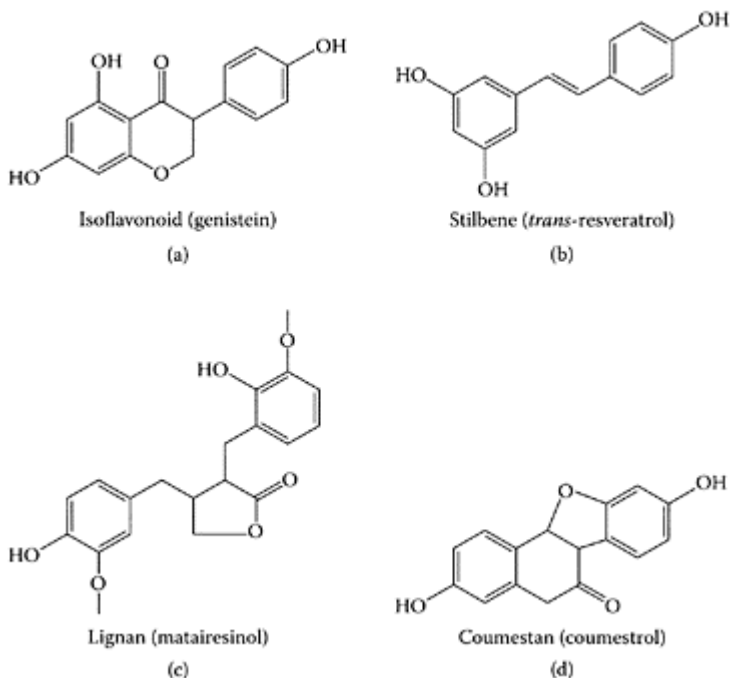
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Phytoestrogens

see also Genistein, Daidzein, and Matairesinol Phytoestrogens are a group of plant compounds that exert both estrogenic and antiestrogenic properties. The four separate plant families of phenolic compounds recognized as phytoestrogens are isoflavonoids, stilbenes, lignans, and coumestans (Scheme P.45). The richest plant sources are isoflavones in soybeans and lignans in flaxseed products (Tham et al., 1998). The anticancer properties of both isoflavonoids and lignans are thought to be responsible for the low incidence of prostate cancers by influencing both endocrine and growth-factor signaling pathways. Phytoestrogens from soybean, genistein and daidzein, were both found by Karamsetty and coworkers (2001) to restore the impaired-relaxation response to nitric-oxide release in pulmonary arteries isolated from chronically hypoxic rats. The latter condition is associated with pulmonary hypertension. For an excellent review of this subject, the article by Cornwell and coworkers (2004) is recommended.

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SCHEME P.45 Structure of phytoestrogens, genistein, coumestrol, *trans*-resveratrol, and matairesinol. (From Cornwell et al., *Phytochemistry*, 65:995–1016, 2004. With permission.)

Phytohemagglutinins

see also Lectins

Phytohemagglutinins (PHA), or lectins, are proteins that bring about the agglutination of red blood cells. They are heat-labile and readily destroyed during normal food processing. Previous studies showed that a diet containing lectin a phytohemagglutinins from raw kidney bean markedly diminished the growth of Krebs II non-Hodgkin lymphoma (NHL) tumors in NMRI mice (Pryme et al., 1994, 1996, 1998). The reduced rate of growth was dose-dependent within the range of 0.45–3.5 mg/g of PHA in the diet (Pryme et al., 1996). Pryme and coworkers (1999) allowed the NMRI mice to develop non-Hodgkin lymphoma tumors for five days prior to feeding different levels of PHA to determine whether feeding the raw kidney lectin was also effective in reducing tumor growth. These researchers found that including PHA in the diet five days after injecting

NHL tumors still reduced the progression of tumor development. This work suggested that further reduction in tumor proliferation might be achieved through manipulation of the diet with PHA and reduced protein.

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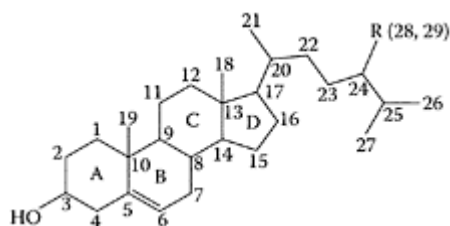
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Phytosterols

Phytosterols are plant sterols differing very slightly in structure from cholesterol by the presence of an ethyl or methyl group at C-24 in the side chain (Scheme P.46). There are more than 100 different phytosterols, but the major ones are β -sitosterol, campesterol, and stigmasterol. Phytosterols stabilize the phospholipid bilayers in plant-cell membranes, as cholesterol does in animal-cell membranes. The fully saturated form of phytosterols (containing no double bond at the 5,6 position) are the phytostanols, which are present in only trace amounts but can also be formed by hydrogenation of phytosterols. On average, we consume approximately 250 mg per day of phytosterols from vegetable oils, cereals, fruits, and vegetables (Hicks and Moreau, 2001; Conner, 1968). In comparison, we consume around 25 mg per day of phytostanols (Conner, 1968; Cerqueira et al., 1979). The ability of phytosterols to lower cholesterol has been well documented (Pollak and Kritchevsky, 1981; Ling and Jones, 1995; Jones et al., 1997; Moghadasian and Frolich, 1999; Law, 2000). In fact, sitosterol was marketed as a drug for lowering cholesterol during the 1950s, but its poor solubility and bioavailability, plus the introduction of “statin” drugs, rapidly diminished its use. Scientists in Finland, however, improved the solubility of phytosterols by esterification which resulted in the first commercial production of phytosterol-containing margarines (Miettinen et al., 1996). Research subsequently showed that 2–3 g/day of phytostanyl ester-containing margarine consistently reduced LDL-cholesterol levels.

Clinical studies on the cholesterol-lowering properties of esterified phytosterols have shown they consistently lower serum LDL cholesterol. Miettinen et al. (1995) showed that consumption of around 23 g/day of a fat spread enriched with 10 percent hydrogenated sterols lowered LDL-cholesterol levels by 10–14 percent. A randomized,

double-blind, placebo-controlled crossover study by Neil et al. (2003) showed patients with heterozygous familial hypercholesterolemia fed a vegetable-oil enriched fat spread reduced LDL cholesterol by 10–15 percent. Mussner and coworkers (2002) found that patients with mild to moderate hypercholesterolemia all had reduced LDL-cholesterol levels



R=H	:Cholesterol
R=CH ₃	:Campesterol
R=C ₂ H ₅	:β-sitosterol
R=C ₂ H ₅ ,Δ ²²	:Stigmasterol

SCHEME P.46 Structure of cholesterol and phytosterols. (From Lea et al., *Food Chem. Toxicol.*, 42:771–783, 2004. With permission.)

when fed a 1.83-g/day dosage of phytosterol esters. The most marked reduction in LDL-cholesterol levels, however, were observed in subjects with a high intake of cholesterol, energy, total fat, and saturated fat and with a high baseline absorption of cholesterol. Bourque and coworkers (2003) showed a combination of dietary ingredients (medium-chain triacylglycerols, phytosterols, and w-3 fatty acids), referred to as a functional oil, significantly lowers total plasma cholesterol and LDL-cholesterol levels in overweight women by 9.1 percent and 16.0 percent, respectively, compared to a beef-tallow-based diet.

The main mechanism responsible for the ability of free and esterified phytosterols to lower cholesterol is inhibition of cholesterol absorption (Trautwein et al., 2003). A recent survey of 9581 participants in Finland by De Jong et al. (2004) showed that of the 31 percent with high cholesterol, 19 percent used cholesterol-lowering drugs, 11 percent used phytosterol-containing spreads, while 5 percent used a combination of both therapies.

Several epidemiological and animal studies indicated that phytosterols may suppress the growth of colonic tumors (Carbin et al., 1990). A randomized, placebo-controlled, double-blind study of 53 men found phytosterols alleviated the symptoms of prostate cancer over a three-month period (Carbin, et al. 1990). A multicentric, placebo-controlled, double-blind clinical trial involving 177 patients showed β-sitosterol as an effective option for treating benign prostatic hyperplasia. Several mechanisms were proposed based on animal-model studies in which phytosterols suppressed the metabolism and growth of the prostate by inhibiting prostatic 5α-reductase and aromatase

activities (Mettlin, 1997; Awad et al., 1998). Inhibition of tumor growth was also explained by the effect of phytosterols on sphingosine metabolism in the membrane, increasing ceramide production with possible alteration of the signaltransduction pathways (Hannun and Linardic, 1993; Wolff et al., 1994). A systematic review of papers published between 1968 and 1998 on the efficacy of β -sitosterol for treating benign prostatic hyperplasia in men by Wilt et al. (1999) showed improvements in urological systems and flow measures. However, these studies were all of short duration, pointing to the need for more long-term studies to assess the efficacy and safety of β -sisterol treatment.

Possible adverse effects of high concentrations of phytosterols could result in cell fragility, particularly in patients suffering from phytosterolemia, a rare genetic disorder with very high concentrations of plasma sitosterols (Patel et al., 2004; Wang et al., 1981). Phytosterols, however, were given generally regarded as safe (GRAS) status in the U.S.A. with the Food and Drug Administration approving fat spreads containing up to 20 percent of either steryl or stanyl esters. For a more detailed discussion of phytosterols, reviews by Moghadasian (2000), Moreau et al. (2002), Tapiero et al. (2003), and Quilez et al. (2003) should be consulted.

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Pine

see also Pycnogenol Pine bark is a medicinal plant used primarily for its proanthocyanidin content. Proanthocyanidins are bioflavonoids with demonstrated antioxidant properties and taken for arthritis, bruises, phlebitis, ulcers, varicose veins, and other vascular problems (Rohdewald, 2002). A pilot study by Shand et al. (2003) showed dietary supplementation with enzogenol, a flavonoid extract from pine bark, was safe and well-tolerated with a number of beneficial effects, including lowering cardiovascular risk

factors. Devaraj et al. (2002) reported an increase in plasma antioxidant capacity and favorable effects on the lipid profile of human subjects treated with extract from pine bark. Pine bark antioxidants may also be helpful in treating hypoxia from arteriosclerosis, inflammation, and cardiac or cerebral infarction (Rohdewald, 2002).

Pycnogenol, a procyanidin extracted from pine bark, is a trademarked, highly standardized extract of pine bark. Supplementation of pycnogenol to patients with conventional diabetes treatment lowered glucose levels and improved endothelial function (Liu et al., 2004). Kim et al. (2004) reported that *Pinus densiflora* bark extracts (out of 1400 tested plants) were the strongest inhibitors of several carbohydratehydrolyzing enzymes, with potential as an antihyperglycemic drug. In mildly hypertensive patients, pycnogenol also significantly reduced the dose of the calcium antagonist nifedipine (Liu et al., 2004).

Roseff (2002) demonstrated pycnogenol therapy improved capacitated sperm morphology and increased the function of normal sperm, suggesting a less invasive and less expensive fertility-promoting procedure. Pycnogenol also proved a useful dietary supplement for *C. pavum*-infected patients, affording some positive health benefits, while significantly reducing oocyst shedding (Kim and Healey, 2001).

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Pinto beans

Pinto beans are excellent sources of fiber. In addition to lowering cholesterol (Bazzano et al., 2003), their high-fiber content prevents blood-sugar levels from rising too rapidly after a meal, making pinto beans a good choice for individuals with diabetes, insulin

resistance, or hypoglycemia (McIntosh and Miller, 2001). The ability of pinto beans to bind bile acids *in vitro* suggests that they may have important, health-promoting properties by lowering cholesterol and the risk of coronary heart disease (Kahlon and Woodruff, 2002).

Marzo and coworkers (2002) showed extrusion cooking significantly ($p<0.01$) decreased the antinutrients, phytic acid, condensed tannins, α -amylase inhibitors, and hemagglutinins. Pretreatment of pinto beans by extrusion cooking improved food intake and utilization in rats by gaining body weight.

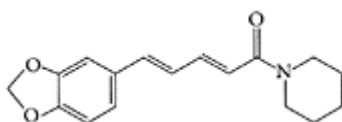
Ye and Ng (2001) isolated peptides from pinto beans with a molecular weight of 5 kDa and an N-terminal sequence similar to cowpea 10-kDa protein precursor. In addition to possessing potent antifungal activity against *Botrytis cinerea*, *Mycosphaerella arachidicola*, and *Fusarium oxysporum*, they also had mitogenic activity toward mouse splenocytes and inhibited HIV-1 reverse transcriptase.

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Piperine

Piperine is the major alkaloid component of black (*Piper nigrum* Linn) and long pepper (*Piper longum* Linn). Previous studies using animal models showed piperine inhibited several cytochrome p450-mediated pathways



Structure of piperine. (From Bajad et al., *J. Chromatogr. B.*, 776:245–249, 2002. With permission.)

and phase II reactions (Atal et al., 1986; Singh et al., 1986). Rodents treated with piperine were found to have an increase in plasma levels of theophylline, phenytoin, rifampin, and propranolol (Atal et al., 1986; Velpandian et al.,

TABLE P.53
Effect of Piperine on the IL-1 β , IL-6, GM-CSF, and TNF- α Production by B16F-10 Melanoma Cells

Cytokine	Control	Piperine (10 μ g/mL)
IL-1 β	185 \pm 8.16 pg/mL	51.66 \pm 6.23 pg/mL*
IL-6	203 \pm 12.47 pg/mL	58.33 \pm 6.28 pg/mL*
GM-CSF	96 \pm 6.97 pg/mL	27.33 \pm 2.49 pg/mL*
TNF- α	191.66 \pm 13.12 pg/mL	53.66 \pm 4.92 pg/mL*

Note: B16F-10 melanoma cells were incubated for 24 h in the presence or absence of piperine (10 mg/mL). Concentrations of IL-1 β , IL-6, GM-CSF, and TNF- α were determined by quantitative ELISA. All experiments were repeated thrice. Values are the means \pm S.D. *Statistically significant from the untreated control: $p < 0.001$.

Source: From Pradeep and Kuttan, *Int. Immunopharmacol.*, 4:1795–1803, 2004. With permission.

2001). Rifampin and phenytoin are both substrates of the drug transporter P-glycoprotein (Schinkel et al., 1996; Schuetz et al., 1996). Bhardwaj and coworkers (2002) showed piperine inhibited both the drug transporter P-glycoprotein and the major drug-metabolizing enzyme CYP3A4. These researchers felt that further work was needed to clarify the impact of piperine on drug disposition in humans.

The anti-inflammatory effect of piperine was shown by Pradeep and Kuttan (2004) by its ability to significantly reduce proinflammatory cytokines, IL-1 β , IL-6, TNF- α , and GM-CSF in B16–10 melanoma cells, as summarized in Table P.53. This was reflected by a marked inhibition of nuclear translocation of c-Fos, ATF-2, and CREB by 28.74 percent, 46.89 percent, and 64.31 percent, respectively. These results suggest that piperine prevents metastasis by targeting transcription factors.

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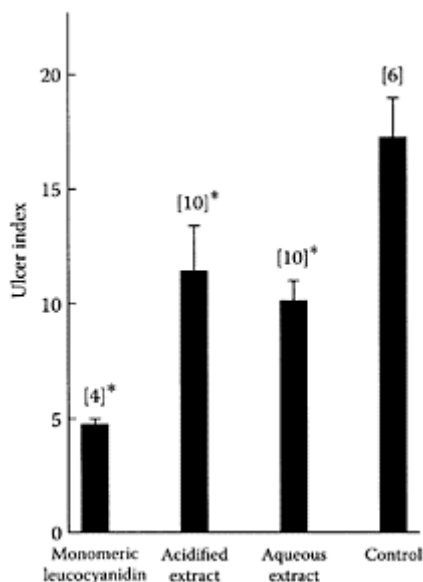
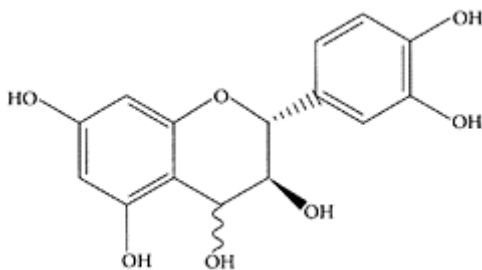


FIGURE P.80 Acute aspirin-induced lesions. The antiulcerogenic potential of the monomeric leucocyanidin (5 mg/day), acidified aqueous extract, and active aqueous extract were derived from 5 g unripe plantain banana. Ulcer index values (Best et al., 1984) are given as the mean±SEM, with the

number of repetitions in parentheses.
Significant differences between
treatments and control diets
determined using the Wilcoxon rank
sum test ($*p<0.05$). (From Lewis et al.,
J. Ethnopharmacol., 65:283–288,
1999. With permission.)

Plantain (*Musa sapientum* L. var. *paradisiaca*)

Plantain bananas, grown extensively in tropical and subtropical countries, can be eaten raw or cooked. Early studies by Elliot and Reward (1976) suggested bananas were antiulcerogenic. Subsequent work confirmed this property in plantain bananas (Best et al., 1984; Goel et al., 1989). Best and coworkers (1984) showed unripe plantain banana protected the gastric mucosa from aspirin-induced damage and that the active agent was polar and readily extracted with warm water or aqueous alcohol. Lewis and coworkers (1999) identified the antiulcerogenic agent in unripe plantain banana as the natural flavonoid, leucocyanidin. Addition of extracted and purified synthetic leucocyanidin in the diet of male Wistar rats significantly ($p<0.05$) protected them from aspirin-induced lesions (Figure P.80). Unfortunately, these beneficial prophylactic effects are lost when plantains are cooked.



Leucocyanidin (3,3',4,4',5,7-hexahydroxyflavan). (From Lewis et al., *J. Ethnopharmacol.*, 65:283–288, 1999. With permission.)

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Platycodon (Platycodon grandiflorum)

Platycodon is an essential herb and a favored ingredient in Chinese medicine. The roots of *Platycodon grandiflorum* have been used as a food or as a traditional oriental medicine for treating bronchitis, asthma, pulmonary tuberculosis, hyperlipidemia, diabetes, and inflammatory diseases (Takagi and Lee, 1972; Lee, 1973). Subsequent studies by Nagao et al. (1986) identified its immunopharmacological properties, while others identified some active compounds, including saponins (Ishii et al., 1984) and triterpenoids (Nikaido et al., 1999). A wide variety of compounds were reported in *Platycodon grandiflorum* by Kim et al. (2000) that exhibited these immunopharmacological properties. Several active compounds, platycodin D (PD) and D3 (PD3) related to oleanolic acid, were isolated from *P. grandiflorum* roots (Tada et al., 1975; Ishii et al., 1978). Using a rabbit macrophage-like cell line, RAW 264.7 cells, Wang et al. (2004) reported both these glycosides were powerful regulators of inflammation by reducing nitric oxide and possessed antitumor activities by stimulating TNF- α synthesis or inhibiting TNF- α mRNA degradation. (See structure for Platycodon on the next page.) Yoon and coworkers (2004) showed that a polysaccharide isolated from *P. grandiflorum* activated macrophages in RAW 264.7 cells, mediated, in part, by mitogen-activated protein kinases (MAPKs) and activator protein-1 (AP-1).

A crude petroleum-ether extract from *P. grandiflorum* was shown by Lee et al. (1998) to be a much stronger inhibitor of human cancer-cell growth compared to an aqueous extract. Further fractionation of this petroleum-ether extract by Lee and coworkers (2004a) separated five fractions (I-V) on a silica-gel column. The phenolic content ranged from 1.66 to 4.80 mg/g, with fraction II containing the highest level. Comparison of their antioxidant activities, based on the formation of TBA, showed that with the exception of fraction I, all other fractions were significantly different ($p < 0.01$) from the control (Figure P.81). Fraction II was the next most effective antioxidant after BHA, with fractions II-IV all exhibiting greater antioxidant activity than α -tocopherol. These data strongly correlated with antioxidant measurements using the ferric-thiocyanate test in which fraction II also proved to be the strongest antioxidant. Using the DPPH free-radical-scavenging test also confirmed FII to be the most potent

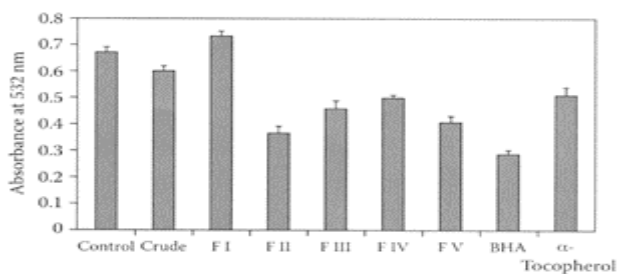
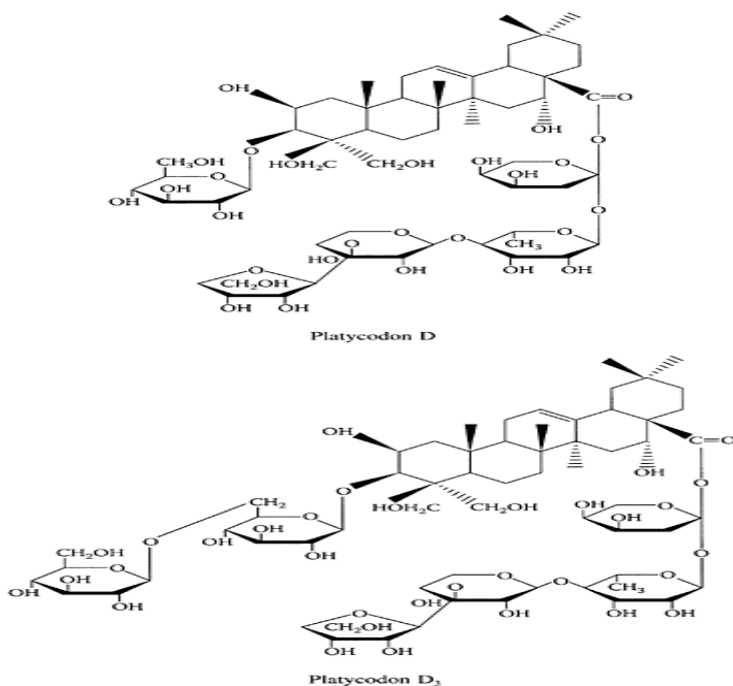


FIGURE P.81 Absorbance at 532 nm of the fractions (F1–V) from *P. grandiflorum* extract by TBA method compared with BHA and α -tocopherol. (From Lee et al., *J. Ethnopharmacol.*, 93:409–415, 2004a. With permission.)



Platycodon D and platycodon D₃. (Wang et al, *Int. Immunopharmacol.*, 4:1039–1049, 2004. With permission.)

DPPH scavenger when present at 100 and 200 mg/mL, followed by FIII. A comparison of their cytotoxicity using three human cancer lines, HT-29, HepG2, and HRT-18,

showed fraction III was the most potent inhibitor. Further work by Lee et al. (2004b) identified coniferyl alcoholic esters of palmitic and oleic acids in fraction II, which may account for its antioxidant properties.

References

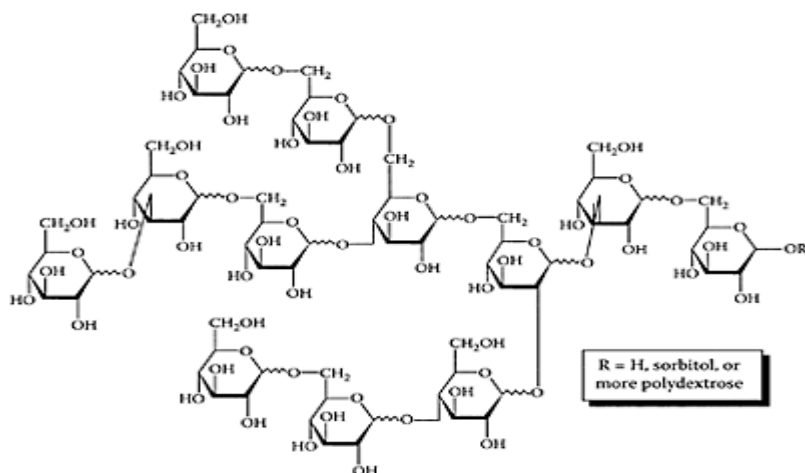
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Polydextrose

Polydextrose, a nondigestible polysaccharide, is prepared by bulk-melt polycondensation of glucose and sorbitol, together with small amounts of food-grade acid *in vacuo* (Flood et al, 2004). The overall product resulting from this random polymerization is a polymer with an average degree of polymerization of 12 with 1,6 glucosidic bonds predominating (Scheme P.47). It was approved as an additive by the FDA in 1982 and is used as a low-calorie bulking agent, replacing sugar in reduced-calorie foods (Mitchell et al., 2001). Polydextrose is often referred to as a resistant oligosaccharide or resistant polysaccharide. As a dietary fiber, it is fermented in the lower gastrointestinal, producing short-chain fatty acids (SCFA), fecal bulking, reduced transit time, and glucose homeostasis (Pfizer, Inc., 1978).

Studies on the physiological effects of dietary polydextrose found it increased calcium absorption (Hara et al., 2000) and retarded lipid transport into the lymph (Ogata et al, 1997). Ishizuka and coworkers (2003) showed ingestion of polydextrose (30 mg/kg) significantly ($p < 0.05$) suppressed formation of aberrant crypt foci (ACF) in the rat colorectum induced by 1,2-dimethylhydrazine (DMH) compared to the fiber-free diet. The earlier the animals were started on polydextrose, the more effective was the treatment in suppressing ACF development (Table P.54).

Flood and coworkers (2004) showed polydextrose was well tolerated and unlikely to induce diarrhea in adults taking less than 50 g per day. The mean laxative threshold dose for



SCHEME P.47 A representative structure for polydextrose. (From Craig et al., *Cereal Foods World*, 43:370–375, 1998. With permission.)

polydextrose (90 g/d or 1.3 g/kg bw) was higher than almost all of the low-caloric carbohydrates on the market.

TABLE P.54
Effect of Polydextrose Ingestion on the Number of ACF in the Rat Colorectum Induced by DMH at Five Weeks After Injection^{1,2}

	Proximal colon	Distal colon	Rectum	Total Colorectum
Fiber-free	ND	29±5	12±2	42±7
Polydextrose A	ND	21±3	5±1*	26±4*
Polydextrose B	ND	24±3	7±1*	30±4
Polydextrose C	0.14±0.14	29±5	7±2*	37±4
Polydextrose D	0.14±0.14	31±4	9±2	40±5

¹ Values expressed as mean ± SEM (n=7).

² Polydextrose A rats were started eight days prior to DMH injection. Polydextrose B rats were started one day prior to DMH injection. Polydextrose C rats were started one day after DMH injection. Polydextrose D rats were started seven days after DMH injection.

* Significantly different from fiber-free-fed group (*p*<0.05).

Source: From Ishizuka et al., *Nutr. Res.*, 23:117–123, 2003. With permission.

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Pomegranate (*Punica granatum*)

The peel of pomegranates was reported to contain large amounts of polyphenols and is used in tinctures, cosmetics, therapeutic formulations, and food recipes (Ben Nasr et al., 1996). The juice of pomegranates was also a rich source of antioxidants (Gil et al., 2000), which accounted for its antiatherogenic effects in humans and animals (Aviram et al., 2000). Using *in vitro* models, Singh et al. (2002) determined the antioxidant activity of ethyl acetate, methanol, and water extracts of pomegranate peels and seeds. Of these, the methanol extract exhibited the greatest antioxidant activity. A recent study by Negi and coworkers (2003) prepared dried powders from peeled pomegranates by Soxhlet extraction with ethyl acetate, acetone, methanol, and water and tested each one for antioxidant and antimutagenic activities. All peel extracts showed potent antioxidant capacity, with the water extract being the lowest. With respect to their antimutagenicity using the Ames test, the order of activity was water extract > acetone > ethyl acetate > methanol. These results suggested pomegranate-peel extracts have considerable potential as nutraceuticals. This was confirmed by Aviram and coworkers (2004) who fed pomegranate juice

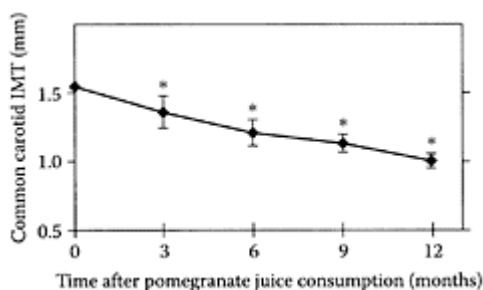
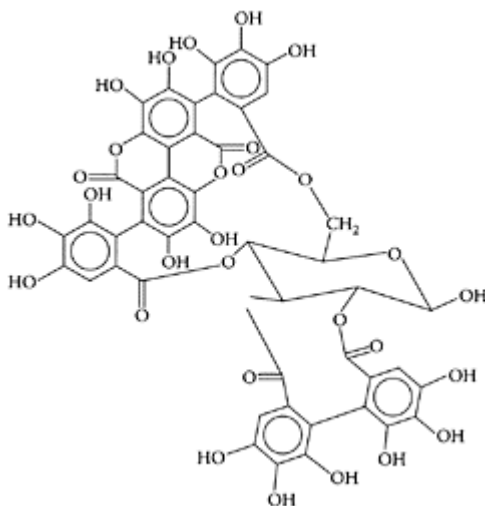


FIGURE P.82 The effect of pomegranate-juice consumption by patients with carotid-artery stenosis on carotid mean intima-media thickness (IMT). Ten patients with severe carotid-artery stenosis were supplemented with pomegranate juice for up to one year, with carotid IMT measured in the patients' left and right carotid arteries before treatment (Baseline) and during pomegranate-juice consumption. (From Aviram et al., *Clin. Nutr.*, 23:423–433, 2004. With permission.)

for a year to 10 patients suffering from carotidartery stenosis, with five of them continuing on for up to three years. In contrast to patients with severe carotid-artery stenosis not consuming pomegranate juice, there was a significant ($p < 0.01$) decrease in the mean intima-media thickness of the left and right common carotid arteries of 13 percent, 22 percent, 26 percent, and 35 percent after 3, 6, 9, and 12 months consumption of pomegranate juice compared to a 9 percent increase for the control (Figure P.82). A significant ($p < 0.05$) decrease in systolic pressure also accompanied pomegranate-juice consumption, with a reduction of 7 percent, 11 percent, 10 percent, 10 percent, and 12 percent after 1, 3, 6, 9, and 12 months of consumption. No significant changes were observed on the patients' diastolic pressure.

Kulkarni et al. (2004) recently isolated and characterized the phenolic compound, punicalagin, from the methanol extract of the pith and carpellary membrane of pomegranate fruit. This compound exhibited potent DPH radical-scavenging activity by donating electrons to free radicals. They suggested that the waste material (pith and carpellary membrane) in pomegranate could be a viable source of this natural and potent antioxidant.



Punicalagin. (From Kulkarni et al., *Food Chem.*, 87:551–557, 2004. With permission.)

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Poppy

The opium poppy, *Papaver somniferum*, is one of man's oldest medicinal plants. Today, opium poppy is a commercial source of narcotic analgesics, morphine and codeine. Along with two morphinans, opium poppy produces approximately 80 alkaloids belonging to various tetrahydrobenzylisoquinoline derivatives. These morphinan alkaloids accumulate in the latex of opium poppy (Weid et al., 2004).

Originally, opium poppies were grown for the pharmaceutical industry for morphine production. However, morphine-free varieties were developed for baking and confectionery purposes. Poppy seeds contain up to 50 percent of a high-quality, semi-drying oil, containing 72 percent linoleic acid, used in artists' paints (Table P.55).

Raw opium contains approximately 25 different alkaloids by weight, depending on the variety. The major alkaloids are morphine (4–21 percent), codeine (0.8–2.5 percent), thebaine (0.5–2.0 percent), papaverine (0.5–2.5 percent), noscapine (0.5–2.5 percent), and meconic acid (3–5 percent). Interaction of poppy alkaloid opioids with endogenous opiate receptors in the

TABLE P.55

Fatty-Acid Composition of Poppy Oil

Fatty Acid	%
Palmitic (C16:0)	10
Stearic (C18:0)	2
Oleic (C16:1)	11
Linoleic (C18:2)	72
Linolenic (C18:3)	5

brain is recognized by clinical pharmacologists for such plants with a long-established medicinal use (Perry et al., 1999). Poppy seeds from *Papaver somniferum* L. were found to contain total morphine (free and bound) in the range of 58.4 to 52.2 micrograms/g of seed and total codeine (free and bound) in the range of 28.4 to 54.1 micrograms/g of seed (Lo and Chua, 1992). Thus, a positive result for morphine in oral fluid may be due to ingestion of poppy seeds (Rohrig and Moore, 2003). However, poppy seeds can also induce immediate-type allergic reactions, ranging from mild, local symptoms to severe anaphylactic reactions, by cross-reacting with other plant-derived allergens (Jensen-Jarolim et al., 1999).

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Pot marigold

Pot marigold (*Calendula officinalis*) is an annual herb with many pharmacological properties. It is used to treat skin disorders and as a bactericide, antiseptic, and anti-inflammatory. The butanol extract of *Calendula officinalis* was shown to have significant radical-scavenging activity (Cordova et al., 2002), which may explain part of its therapeutic efficacy. Dichloromethane extracts of its flowers were shown to contain eight known bioactive triterpenoid monoesters (Neukirch et al., 2004). Faradiol 3-O-laurate, palmitate, and myristate were identified as the major anti-inflammatory triterpenoid esters in the flower heads of *Calendula officinalis* (Hamburger et al., 2003).

The main carotenoids found in the petals and pollens of *Calendula officinalis* were flavoxanthin and astaxanthin, while the stems and leaves contained mostly lutein and β -carotene (Bako et al., 2002). Calendasaponins A, B, C, and D, ionone glucosides

(officinosides A and B), and sesquiterpene oligoglycosides (officinosides C and D) were all isolated from the flowers of Egyptian *Calendula officinalis* exhibiting hypoglycemic, gastric emptying inhibitory, and gastroprotective effects (Yoshikawa et al., 2001).

Perez-Carreón et al. (2002) demonstrated the chemopreventive properties of *Calendula officinalis* extracts by their antigenotoxic effects on rat liver cell cultures treated with diethylnitrosamine. At higher concentrations, however, they proved genotoxic. In a phase III randomized trial, Pommier et al. (2004) found *Calendula officinalis* was an effective, nonsteroid topical agent for preventing acute dermatitis during adjuvant radiotherapy for breast carcinoma compared to the drug trolamine. They proposed its use for patients undergoing postoperative irradiation for breast cancer.

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Potato

Antioxidant activity in potatoes is supported by the findings of free and bound phenolics (Chu et al., 2002). In particular, potato peel, a waste product from potato processing, was found to be rich in phenolic acids (Lisinska and Leszczynski, 1987) and later shown to be a source of antioxidants in food systems (Rodriguez et al., 1994). Rehman et al. (2004) recently examined a petroleum-ether extract from potato peels that exhibited strong

antioxidant activity and enhanced the shelf life of soybean oil. The free-radical-scavenging activity of a freeze-dried aqueous extract of potato peel was confirmed by Singh and Ranjini (2004) using 1,1-diphenyl-2-picrylhydrazine (DPPH). They also reported it strongly inhibited lipid peroxidation of rat liver homogenates induced by the $\text{FeCl}_2\text{-H}_2\text{O}_2$ system. Further work is needed to ensure the safety and efficacy of the antioxidants from potatoes and potato peels in relation to their potential as sources of nutraceuticals.

Morita et al. (1997) reported lower serum total-cholesterol concentrations in rats fed potato proteins compared to those fed casein. Schafer et al. (2003) later showed potatoes, as a carbohydrate source, elicited significantly better glycemic and insulinemic responses in patients with type 2 diabetes compared to dried peas.

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Prebiotics

see also Acacia gum, Arabinosyran, Fructooligosaccharides, and Inulin Prebiotics are oligosaccharides that promote the growth of beneficial bacteria in the GI tract. These include inulin-type fructans, which include native inulin, hydrolyzed inulin, or oligofructose and synthetic fructooligosaccharides (Roberfroid, 1998; Roberfroid et al., 1998).

Human milk oligosaccharides represent the first prebiotics in humans, as they are only partially digested in the small intestine. Once they reach the colon, they selectively stimulate the development of the bifidogenic flora (Coppa et al., 2004). A bovine-milk formula supplemented with a prebiotic mixture of galactooligosaccharides and

fructooligosaccharides can stimulate an intestinal flora, similar to that of breast-fed infants. Several biota, whose growth is enhanced by this prebiotic mixture, represent important factors in the postnatal development of the immune system (Boehm et al., 2004).

Dietary modulation of the gut microflora by prebiotics is designed to improve health by stimulating the numbers and activities of the bifidobacteria and lactobacilli. Having an “optimal” gut microflora can increase resistance to pathogenic bacteria, lower blood ammonia, increase stimulation of the immune response, and reduce the risk of cancer (Manning and Gibson, 2004). Thus, the physiological consequences of prebiotic consumption are evaluated in terms of potential to reduce risk for disease. Most research has been done with $\beta(2-1)$ fructans as an example of prebiotics. These results are relevant in the fields of gut function, lipid metabolism, mineral absorption, bone formation, immunology, and cancer (Van Loo, 2004).

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Probiotics

Probiotics are bacteria that keep disease-causing organisms in check. For example, *Lactobacillus acidophilus* is added to yogurt while *Lactobacillus reuteri* and *Lactobacillus bifidus* also promote health. Probiotics are viable microbial food ingredients that have a beneficial effect on the intestinal tract of their host (Salimen et al., 1998). Most probiotics are lactobacilli and bifidobacteria, presently consumed almost exclusively as fermented dairy products, such as yogurts or freeze-dried cultures. These probiotics survive the digestive process and become established in the large bowel with recognized benefits (Sanders, 1993; Marteau and Rambaud, 1993; Salimen et al., 1996). Studies have shown probiotics may be effective in reducing diarrhea (Isolauri et al., 1991; Corthier, 1997; Allen et al., 2004). Other studies suggest probiotics could help in managing clinical inflammatory-bowel disease (Fedorak and Madsen, 2004) and in treating functional abdominal bloating (Di Stefano et al., 2004).

Steatohepatitis is recognized as the leading cause of cryptogenic cirrhosis, although the pathogenesis of this disease is not fully understood. Nevertheless, among various factors implicated, intestinal bacterial overgrowth may be involved. Thus, probiotic treatment may be beneficial (Nardone and Rocco, 2004).

Studies examining the use of probiotics in food allergy, atopic dermatitis, and in the primary prevention of atopy found probiotic therapy alleviated allergic inflammation by controlling symptoms and reducing local and systemic inflammatory markers (Miraglia del Giudice and De Luca, 2004).

Probiotics may also improve lactose absorption and *Helicobacter pylori* eradication and constipation. In animal models with colorectal cancer, treatment with probiotics reduces the prevalence of this disease, while in humans, the amount of genotoxic substances in the feces are reduced (Goossens et al., 2003).

In summary, the potential benefits of probiotics include: adherence to cells; exclusion or reduction of pathogenic adherence; production of acids, hydrogen peroxide, and bacteriocins antagonistic to pathogen growth; safe, noninvasive, noncarcinogenic, and nonpathogenic characteristics; and congregate to form a more balanced intestinal flora (Otles et al., 2003).

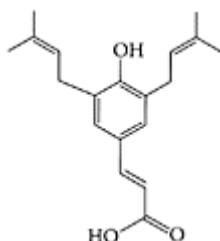
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Propolis or bee glue

Propolis or bee glue, a resinous plant material collected by honeybees from the buds and bark of certain plants and trees, may serve as a defense for their hives (Ghisalberti, 1979). A number of health benefits have been ascribed to propolis, including anticancer (Matsuno, 1995), antimicrobial (Koo et al., 2000), anti-inflammatory, and antibiotic (Bianchini and Bendendo, 1998) properties. Propolis contains many different types of flavonoids and cinnamic-acid derivatives, some of which are known antitumor agents. One of the components identified by Matsuno et al. (1997) was artepillin C (3,5-diprenyl-4-hydroxycinnamic acid). This compound was shown to reduce tumors in experimental-animal models



Artepillin C. (From Uto et al., *J. Org. Chem.*, 67:2355–2357, 2002.)

(Kimoto et al., 2000, 2001). The antimutagenic properties of an ethanol extract of bee glue or propolis (EEGB) against a number of environmental mutagens was demonstrated by Jeng and coworkers (2000). These researchers reported EEGB suppressed the mutagenicity of two direct mutagens, 4-nitro-*O*-phenylenediamine (4-NO) and 1-nitropyrene (1NP), and two indirect mutagens, 2-amino-3-methylimidazo[4.5-*f*] quinoline (IQ) and benzo[*a*]pyrene (B[*a*]P) in a dose-dependent manner. Sugimoto et al. (2003) recently examined the inhibitory effects of propolis granular A.P.C., an extract containing more than 35.8 µg artepillin C/g, on female A/J mice lung tumors induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), one of the most potent carcinogens among tobacco-specific nitrosamines. While lungtumor incidence was not affected by propolis, tumor multiplicity was significantly ($p < 0.01$) reduced by 72 percent. No adverse effects were

TABLE P.56**Lipid Levels in Serum of Rats Given Alcohol and Alcohol+Propolis for 15 Days**

Parameters	Groups		
	Control	Alcohol	Alcohol+Propolis
HDL (mg/dL)	37.0±0.96	7.85±3.7 ^a	29.8±1.1 ^a
LDL (mg/dL)	5.8±0.73	19.0±4.17 ^{a, b}	4.28±1.44
VLDL (mg/dL)	21.5±1.43	29.3±4.03	22.7±2.94
Cholesterol (mg/dL)	62.6±1.83	53.8±1.19 ^{a, b}	49.0±1.54 ^a
Triglyceride (mg/dL)	148±7.66	146±20.2 ^b	114±14.8 ^a

^a Significantly different from control group ($p \leq 0.05$). ^b Significantly different from propolis group ($p \leq 0.05$).

Source: From Kolankaya et al., *Food Chem.*, 78:213–217, 2002. With permission.

observed from propolis granular A.P.C., suggesting possible clinical applications. Further research is warranted to substantiate the role of artemillin C and other components in the antitumor properties of propolis A.P.C.

Kolankaya and coworkers (2002) reported that Turkish *Castenea saliva* propolis exerted a protective effect against degenerative diseases and alcohol-induced oxidative stress. In the presence of propolis treatment, the alcohol-induced oxidative stressed male rats had increased HDL and decreased the LDL levels compared to the alcohol-induced stressed animals (Table P.56).

In addition, the activity of LDH enzyme increased in the presence of propolis compared to the control. These researchers suggested that propolis exerted its protective effect against degenerative diseases through its protection against free radicals.

Matsui and coworkers (2004) showed a single, oral administration of propolis extract to Sprague-Dawley rats had a potent antihyperglycemic effect, with a significant reduction of 38 percent at a dose of 20 mg/kg compared to the control. Among the active compounds isolated from this fraction, 3,4,5-tri-*O*-caffeoylquinic acid, proved to be most prominent.

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Prostaglandins

Prostaglandins are bioactive lipids produced from arachidonic acid. They are found in many vertebrate tissues, where they act as messengers involved in reproduction and inflammatory response to infection. They exert an autocrine-paracrine function by attaching to specific prostanoid G protein-coupled receptors to activate intracellular signaling and gene transcription. For many years, prostaglandins were recognized as key molecules in reproductive biology by regulating ovulation, endometrial physiology, and proliferation of endometrial glands and menstruation (Sales and Jabbour, 2003). More recently, a role in reproductive tract pathology was reported, including carcinomas, menorrhagia, dysmenorrhoea, and endometriosis. Although the mechanism by which prostaglandins modulate these pathologies is still unclear, a large body of evidence

supports a role for them in angiogenesis, apoptosis and proliferation, tissue invasion, and metastases and immunosuppression (Martel-Pelletier et al., 2004).

Prostaglandins thus act on a variety of cells, such as vascular smooth muscle cells, causing constriction and dilation, on platelets causing aggregation or disaggregation, and on spinal neurons causing pain. Other effects can be calcium movement, hormone regulation, and cellgrowth control. Certain prostaglandins are involved with induction of labor and other reproductive processes. For example, PGE2 causes uterine contractions and has been used to induce labor. Prostaglandins are also involved in several other organs, such as the gastrointestinal tract (inhibiting acid synthesis and increasing secretion of protective mucus), increases blood flow in the kidneys, and leukotrienes, which promote constriction of bronchi associated with asthma. A recent review by Prisk and Huard (2004) examines the role of prostaglandins and their potential for therapeutic interventions.

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Protease inhibitors

see Bowman-Birk protease inhibitor and Trypsin inhibitors

Proteins

see Amaranth, Casein, Quinoa, and Soybean

Prunes

Prunes (*Prunus domestica* L.) are a good source of dietary fiber, as well as phenolic compounds, ascorbic acid, and carotenoids (Bravo, 1998). The dietary fiber in prunes is

TABLE P.57
Proximate Analysis of Prune Powder

Component	Amount Per 100 Gram Portion
Protein	3.0
Fat	0.5
Total carbohydrates	80.0
Total dietary fiber	9.0

Source: Adapted from Lucas et al., *J. Nutr. Biochem.*, 11:255–259, 2000.

composed mainly of pectin (60 percent). The major components of prune powder are shown in Table P.57. Lucas et al. (2000) reported that inclusion of 25 percent prunes in the diets of ovariectomy-induced hypercholesterolemic rats prevented a rise in serum, total, and non-HDL cholesterol concentrations.

Prunes are particularly well known for their laxative action, which is explained by their high sorbitol content. They are also a good source of energy in the form of simple sugars but do not mediate a rapid rise in blood sugar, possibly because of their high fiber, fructose, and sorbitol content. The large amounts of phenolic compounds (184 mg/kg) in prunes may aid their laxative action and delay glucose absorption (Kikuzaki et al., 2004). Phenolic compounds in prunes have also been found to inhibit human LDL oxidation *in vitro*, and thus might serve as preventive agents against chronic diseases, such as heart disease and cancer (Kayano et al., 2003). In addition, the high potassium content of prunes (745 mg/100 g) might be beneficial for cardiovascular disease. Dried prunes are also an important source of boron, which is postulated to play a role in the prevention of osteoporosis (Stacewicz-Sapuntzakis et al., 2001).

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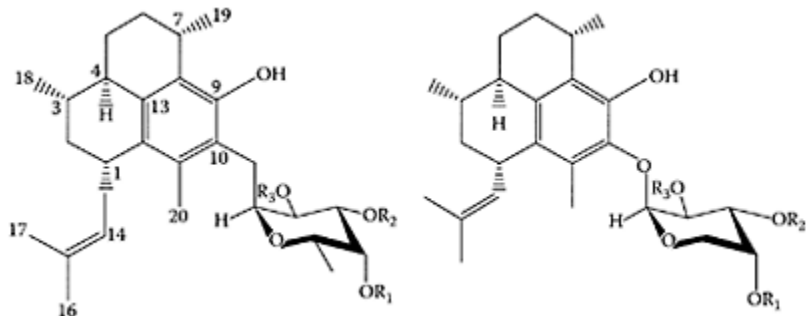
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Pseudopterosins

Pseudopterosins are diterpeneglycosides isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae* (Octocrallia, Cnidaria). They have been shown to possess anti-inflammatory and analgesic properties (Look et al., 1986). Pseudopterosin A, a C-9 xylose glycoside isolated from the marine gorgonian *Pseudopterogorgia elisabethae*, was found to be effective in reducing PMA-induced mouse-ear edema when administered topically. Mayer et al. (1998) showed it inhibited prostaglandin ER2 and leukotriene C4 production in zymosan-stimulated murine peritoneal macrophages, suggesting pseudopterosin A mediated anti-inflammatory effects by inhibiting eicosanoid release from inflammatory cells. The nonsteroidal, anti-inflammatory, and analgesic properties of pseudopterosins were shown to be greater than the industry standard drug, indomethacin. This led investigators to examine the biosynthesis and enzymology of these compounds to develop a biotechnology production method (Kohl et al., 2003). Ata and coworkers (2003) identified a number of new pseudopterosins and seco-pseudopterosins from marine gorgonian *Pseudopterogorgia elisabethae*, as well as a novel hydroxyquinone, elisabethadione. The anti-inflammatory properties of the latter, however, proved more potent than either pseudopterosin A or E. Seven new pseudopterosins, P-V, were identified recently by Duque et al. (2004) from gorgonian octocoral



1: R₁, R₂, R₃=H 2: R₁=Ac, R₂, R₃=H 3: R₂=Ac, R₁, R₃=H 4: R₃=Ac, R₁, R₂=H

5: R₁, R₂, R₃=H 6: R₁=Ac, R₂, R₃=H 7: R₂=Ac, R₁, R₃=H

SCHEME P.48 New pseudopterosins isolated from *Pseudopterogorgia elisabethae* from Providencia island, Colombian Caribbean. (From Duque et

al., *Tetrahedron*, 60:10627–10635, 2004. With permission.)

Pseudopterogorgia elisabethae from Providencia Island in the Colombian Caribbean, as shown in Scheme P.48. However, their health-related properties still remain to be studied.

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Psyllium

Psyllium is the mucilage obtained from the seed coat (husk or hull) of the plant genus *Plantago*. It has a long history of medicinal use because of its cholesterol-lowering, laxative, gastro-hypoacidity, and possibly weight-control properties (Anderson et al., 1990; Arjmandi et al., 1992; Hara et al., 1996; Park et al., 1997). A meta-analysis of 12 studies involving 404 adults with mild to moderate hypercholesterolemia by Olson et al. (1997) concluded that psyllium reduced total and LDL cholesterol by 5 percent and 9 percent, respectively. A study on 125 patients with type 2 diabetes by Rodriguez-Moran et al. (1998) found that treatment with 5 grams of psyllium t.i.d. over six weeks significantly reduced ($p<0.05$) fasting plasma glucose (Figure P.83), as well as total plasma cholesterol, LDL cholesterol, and triglycerides, while significantly increasing ($p<0.01$) HDL cholesterol.

Fang (2000) showed that psyllium improved the serum-lipid profiles in Sprague-Dawley rats by reversing the hypercholesterolemic effects of *trans* fatty acids. Recently, Marlett and Fischer (2003) reported that a gel-forming component in psyllium seeds, which was not fermented, was responsible for its laxative and cholesterol-lowering properties. The active fraction was a highly branched arabinoxylan consisting of a xylose backbone and arabinose- and xylose-containing side chains.

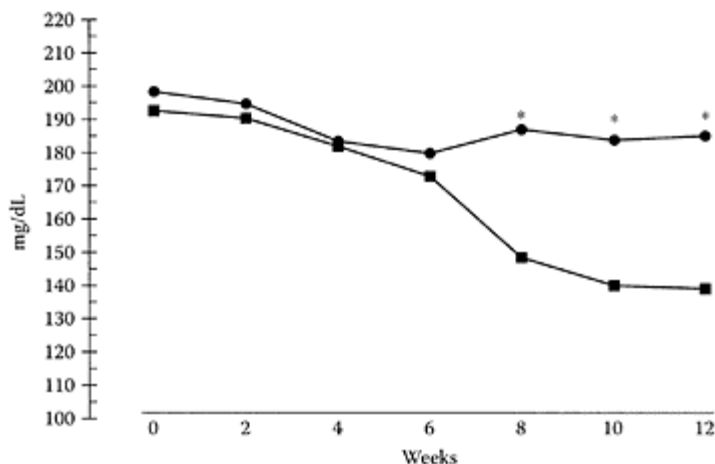


FIGURE P.83 Mean plasma-glucose levels. In the period of diet counseling (weeks 0–6), there were mild but not significant variations on glucose levels for both groups. The treatment beginning at week 6, and during all this period (to week 12), the patients on psyllium group (■) showed a greater and statistically significant reduction in plasma-glucose levels compared to the placebo group (●). Asterisk indicates a significant difference at $p < 0.01$. (From Rodriguez-Moran et al., *J. Diab. Comp.*, 12:273–278, 1998. With permission.)

Psyllium was shown to improve glucose homeostasis and the lipid and lipoprotein profiles in obese children and adolescents with abnormalities in carbohydrate and lipid metabolism (Moreno et al., 2003). Beneficial, therapeutic effects reported for psyllium include the metabolic control of type 2 diabetes, as well as lowering the risk of coronary heart disease (Sierra et al., 2002).

The synergistic effect of wheat bran and psyllium was shown by Albaster et al. (1993) to inhibit the early phases of carcinogenesis. Cohen et al. (1996) also reported the effects of wheat bran and psyllium diets in reducing *N*-methylnitrosourea-induced mammary tumorigenesis in F344 rats. The antitumor activity of psyllium was recently demonstrated by Nakamura et al. (2004), who showed it restored normal gap junctional intercellular

communication (GJIC) and anchorage-independent growth (AIG) by reversing two tumor-cell phenotypes induced by the *Ha-ras* oncogene.

While no adverse effects have been associated with psyllium intake, nevertheless some individuals may be allergic to it (James et al., 1991). In addition, Luccia and Kunkel (2002) showed that an increase in soluble fiber from sources such as psyllium reduced calcium bioavailability in weanling Wistar rats, as well as had negative effects on bone composition. The increased consumption of psyllium, however, has since led to its recognition as an emerging food allergen (Khalili et al., 2003)

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Pulses

see also Beans, Lentils, and Soybeans Pulses are the health-promoting, edible seeds of leguminous plants grown for food and include peas, beans, and lentils (Messina et al., 1999). The nonnutrient, bioactive agents in pulses were reviewed by Champ (2002). While many were considered antinutritional factors, subsequent research suggests many of these compounds may play a role in the prevention of chronic diseases. A list of these compounds can be found in Table P.58.

Anderson and Major (2002) reviewed both the epidemiological and clinical data, which supported the hypocholesterolemic effect of soybean and pulses. In addition, they performed a meta-analysis of 11 clinical trials that showed pulses decreased cholesterol and LDL cholesterol while increasing HDL cholesterol. These effects were attributed to the presence of soluble dietary fiber, protein, oligosaccharides, isoflavones, phospholipids, fatty acids, and

TABLE P.58
Major Nonnutrient Bioactive Pulse Compounds

Bioactive Component	Possible Beneficial Effects
Amylase inhibitors	Diabetes treatment
Lectins	Obesity and tumors
Phenolic compounds	
Flavonoids, isoflavones	Menopause and anticancer
Lignans (phytoestrogens)	Menopause
Protease inhibitors	Anticarcinogenic
Saponins	Hypocholesterolemic, anticancer
Source: Adapted from Champ, <i>Br. J. Nutr.</i> , 88:S307–S319, 2002.	

saponins. Additional benefits included reduction in blood pressure, glycemia, and the risk for obesity.

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Messina, M.J., Legumes and soybeans: An overview of their nutritional profiles and health effects, *Am. J. Clin. Nutr.*, 70:439S-450S, 1999.

Purple corn color

Purple corn color (PCC) is a natural anthocyanin pigment that was found by Hagiwara and coworkers (2001) to have anticancer properties. When fed at a dietary level of 5 percent to male F344/DuCrj rats, pretreated with 1,2-dimethylhydrazine (DMH) to develop colorectal carcinogenesis, it suppressed lesions, as well as decreased the induction of aberrant crypts by the presence of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) in the diet.

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Hagiwara, A., Miyashita, K., Nakanishi, T., Sano, M., Tamano, S., Kadota, T., Koda, T., Nakamura, M., Imaida, K., Ito, N., and Shirai, T., Pronounced inhibition by a natural anthocyanin, purple corn color, of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)-associated colorectal carcinogenesis in male F344 rats pretreated with 1,2-dimethylhydrazine, *Cancer Lett.*, 171:17–25, 2001.

Pycnogenol

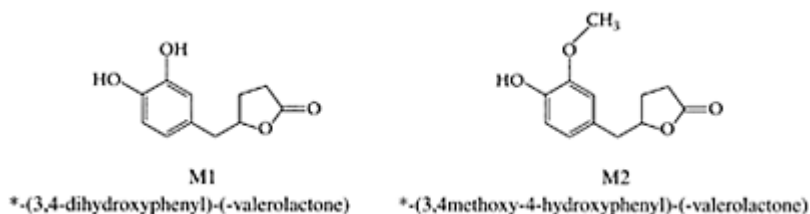
Pycnogenol is a mixture of oligomeric and monomeric procyanidins isolated from the bark extract of French maritime pine (*Pinus pinaster*) (Masquelier, 1997). Composed of water-soluble procyanidins, catechin, taxofolin, and phenolcarbonic acid, it is used as a dietary supplement. Hosseini et al. (2001) showed Pycnogenol® (200 mg/day) lowered diastolic blood pressure, but not statistically, in mildly hypertensive patients. However, serumthromboxane levels were reduced significantly during treatment.

Using a rat pheochromocytoma (PC 12) cell line, Peng et al. (2002) found Pycnogenol® protected neurons from amyloid- β peptide-induced apoptosis, one of the pathological features associated with Alzheimer's disease. Pycnogenol decreased the percentage of apoptotic cells and inhibited caspase-3 activation, DNA fragmentation, and poly(ADP-ribose) polymerase (PARP) cleavage. The possible involvement of oxidative stress was evident by Pycnogenol's suppression of amyloid- β peptide's generation of reactive-oxygen species (ROS), as evident in the presence of vitamin E. Thus, the antioxidant properties of Pycnogenol® appeared partly responsible for reducing these cells from amyloid- β peptide's neurotoxicity. Huang et al. (2005) recently reported

Pycnogenol® induced differentiation and apoptosis in human promyeloid leukemia HL-60 cells, suggesting it could act as a potent cancer chemopreventive or chemotherapeutic agent.

The role of ROS in inflammatory processes, such as rheumatic diseases, led to a recent study by Grimm et al. (2004) on matrix-degrading enzymes, matrix metalloproteinases (MMPs). MMPs are a family of zinc-dependent proteolytic enzymes activated by ROS that contribute to the inflammatory network (Visse and Nagase, 2003; Rajagopalan et al., 1996). Two major metabolites of the standardized pine-bark extract Pycnogenol®, M1 and M2, were identified by Grosse-Duweler and Rohdewald (2000), with strong reducing power (Scheme P.49). Grimm et al. (2004) showed M1 and M2 strongly inhibited matrix metalloproteinase MMP-1, as shown in Figure P.84. Similar inhibitory effects were also observed on MMP-2 and MMP-9. M1 proved a more effective scavenger of superoxide than (+)-catechin, ascorbic acid, and trolox, while M2 had no scavenging activity. These results point to the potential prophylaxis and therapeutic uses of Pycnogenol® in disorders resulting from an imbalance or excess of metalloproteinase activity.

Recent research by Liu et al. (2004a) suggested that supplementation of mildly hypertensive patients with Pycnogenol® significantly reduced the dosage of the antihypertensive drug, nifedipine. A double-blind, placebo-controlled, randomized, multicenter study by Liu et al. (2004b) on 77 diabetes type 2 patients



SCHEME P.49 The two main metabolites of Pycnogenol® identified in human urine. (From Grosse-Duweler and Rohdewald, *Pharmazie*, 55:364–368, 2000. With permission.)

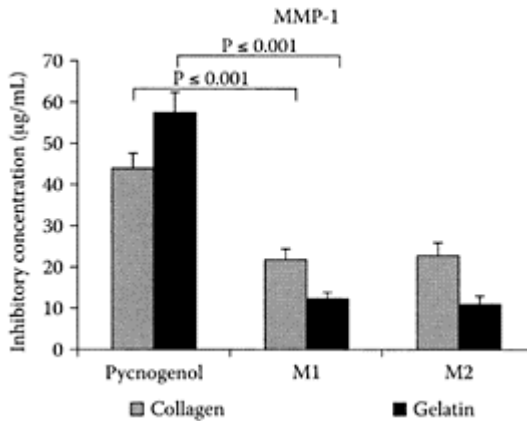


FIGURE P.84 Mean concentrations of Pycnogenol[®], M1, and M2 that produced 50 percent inhibition of MMP-1 activity toward degradation of collagen or gelatin, respectively. Each column represents the mean and SD of six independent experiments. Statistically significant differences between compounds are shown only for metabolite M1 (ANOVA with subsequent Tukey test). (From Grimm et al., *Free Rad. Biol. Med.*, 36:811–822, 2004. With permission.)

also showed multiple benefits were derived from supplementation with 100 mg Pycnogenol[®] over 12 weeks, including significantly lowering of plasma-glucose levels. Other benefits included inhibiting endothelin-1 production, expression of adhesion molecules, and platelet aggregation.

Durackova et al. (2003) found Pycnogenol[®] was beneficial in the treatment of erectile dysfunction, as well as improving the atherogenic factor of lipoproteins and antioxidant status of plasma. Mantle et al. (2005) recently noted pycnogenol was part of a nutritional supplement that included calcium, carnitine, coenzyme Q₁₀, glucosamine, magnesium, methyl sulfonyl methane, silica, vitamin C, and vitamin K, which proved effective in treating Ehlers-Dantos syndrome, a rare, inherited disorder of the connective tissue.

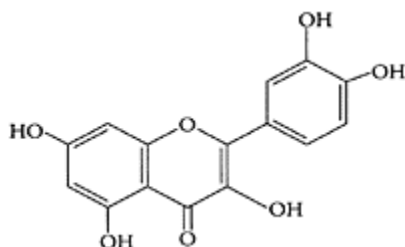
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Q

Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the most abundant bioflavonoids in edible fruits and vegetables, with an estimated daily intake of 25–50 mg (Formica and Regelson 1995). It is associated with little toxicity when administered orally or



Quercetin. (From Igura et al., *Cancer Lett.*, 171:11–16, 2001. With permission.)

intravenously. Quercetin is a potential anticancer agent through its cell-cycle regulation, interaction with type II estrogen-binding sites (Shenouda et al., 2004), and inhibition of tyrosine kinase. *In vitro* studies showed quercetin inhibited tumor growth and proliferation of tumor cells by reducing the number of aberrant crypt foci (Lamson and Brignall, 2000). A possible mechanism is that quercetin upregulates expression of several tumor-suppressor genes (Nair et al., 2004; Van Erk, 2004). A recent study by Mertens-Talcott and Percival (2005) reported a synergistic interaction between quercetin and ellagic acid with resveratrol in the induction of apoptosis and cell-cycle kinetics in a human leukemia-cell line (MOLT-4). For example, caspase-3 activation, which precedes apoptosis, was induced in 35 percent of the treated cells (EC_{35}) by 12.8 mmol/L for quercetin, 54.0 mmol/L for resveratrol, and 68.4 mmol/L for ellagic acid (Figure Q.85A). The EC_{35} for the combinations of quercetin:resveratrol and ellagic acid:resveratrol were 6.4 mol/L and 16.9 mol/L, respectively (Figure Q.85B).

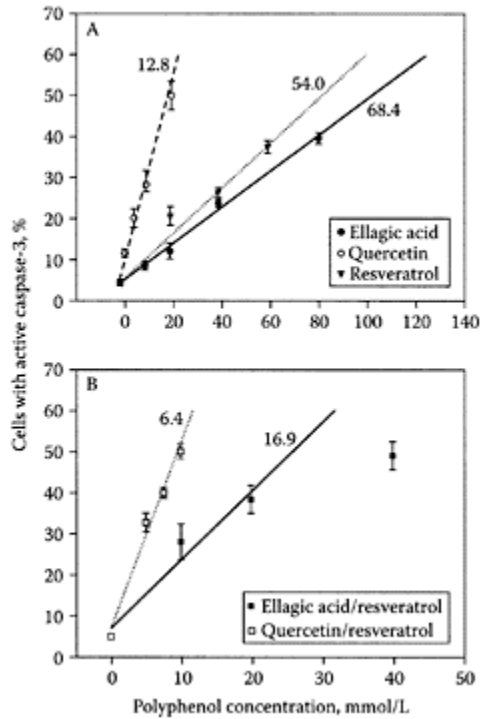


FIGURE Q.85 Caspase-3 activity in MOLT-4 cells after 10 h of treatment with ellagic acid, quercetin, or resveratrol (A) and 1:1 combinations of these (B). Values are means+SEM, n=4. Numbers above each data line represent the EC₃₅, as determined by linear regression. *The line was generated from the linear portion of the curve; therefore, the value induced by the highest concentration was not included in the calculation. (From Mertens-Talcott and Percival, *Cancer Lett.*, 218:141–151, 2005. With permission.)

Epidemiological studies point to a crucial role for quercetin in the prevention of cardiovascular disease. There is an inverse relationship between dietary flavonoids, particularly quercetin, and the risk of cardiovascular disease (Hertog et al., 1993). This

protective effect is attributed to quercetin's antioxidant capacity and its inhibition of LDL oxidation *in vitro* (Janisch et al., 2004). The antiproliferative and antimutagenic activities of quercetin *in vitro* have made it a candidate for clinical trials in cancer therapy (Hertog, 1996).

Cornish et al. (2002) showed quercetin played a possible role in reducing the incidence of cataracts by inhibiting oxidative damage in rat lenses. Using the LOCH model, quercetin was converted by catechol-*O*-methyltransferase (COMT) in the rat lenses to its metabolite, 3-*O*-methyl quercetin, both of which inhibited hydrogen peroxide-induced opacification.

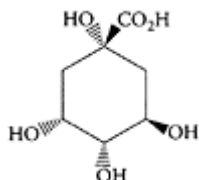
Muthian and Bright (2004) found quercetin ameliorated experimental allergic encephalomyelitis by blocking IL-12 signaling and Th1 differentiation, suggesting it may be effective in treating multiple sclerosis and other Th1-cell-mediated autoimmune diseases.

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Quinic acid

see also Cat's claw Quinic acid, a water-soluble, organic acid, is a metabolite of the shikimic-acid pathway in plants. Akesson et al. (2005) identified quinic acid as the active component in the hot-water extract (C-Med-100®)



Quinic acid. (Adapted from Banwell et al., *Org. Lett.*, 6:2737–2740, 2004.)

from the bark of Cat's Claw (*Uncaria tomentosa*). The water extract from *U. tomentosa* has been associated with the anti-inflammatory properties of Cat's Claw (Aquino et al., 1991; Lemaire et al., 1999). While the content of free quinic acid was low in the water extract, it was present in the form of esters. Quinic acid was shown to inhibit NF-κB in cells grown in tissue culture *in vitro* by a different mechanism than C-Med-100®. Recent work by Sheng and

TABLE Q.59

The Coupling of the Disappearance of *In Vitro* Biological Efficacy of C-Med-100 Assessed in HL-60 and HML Cells to a Corresponding Disappearance in CAE Content Analyzed as QA Esters by the Bartos Reaction

Compound	HL-60 MTT IC ₅₀ (μg/mL)	HML MTT 2x #cells (μg/mL)	%QA est. (Bartos)	QA est. TLC Identical
QA	2300	>2300	0	++++
QAL	2300	>2300	100	0
QAL+2MNaOH, 2 h	1900	>2300	35	++
C-Med-100 (no base hydrolysis)	536	500	4.7	±
C-Med-100 (M NaOH for 2 h)	900	1200	2.5	++

Source: From Sheng et al., *J. Ethnopharmacol.*, 96:577–584, 2005. With permission.

coworkers (2005) showed the active ingredients in C-Med 100® were carboxyl alkyl esters (CAEs), that enhance DNA repair and immune cell responses. Their disappearance was responsible for the loss in biological efficacy of C-Med-100®. Thus the data presented in Table Q.59, in which quinic-acid lactone (QAL) and C-Med-100® preparations were far more effective in reducing the growth of human leukemic cells (HL-60) and human mononuclear leukocytes (HML). This was assessed using the MTT vital staining colorimetric bioassay, which is only taken up by the viable cells but cannot distinguish between those replicating and not replicating.

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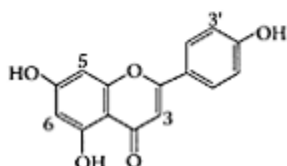
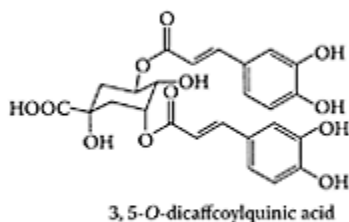
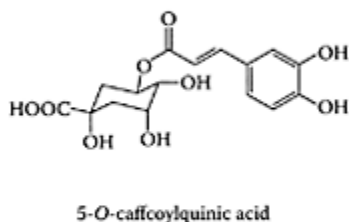
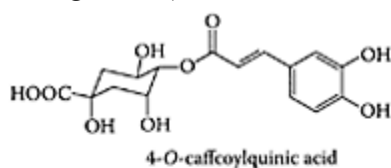
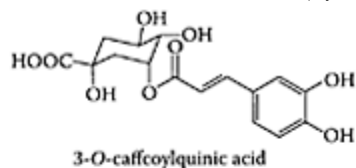
Quince

Quince (*Cydonia oblonga* Miller) is a pome fruit of a deciduous tree of the *Rosaceae* family. The fruit is inedible due to its hardness, bitterness, and astringency and is generally processed and used for its jam, called “marmaleda” (Silva et al., 2005).

The antioxidant activity of quince was examined by Silva et al. (2004). The wide array of phenolic compounds identified in quince fruit and jam are shown in Scheme Q.50. In addition, seven organic acids were also identified, including ascorbic, shikimic, quinic, oxalic, citric, malic, and fumaric acids. The strongest antioxidant activity was observed in the peel, while the pulp and seed exhibited lower but similar activities. The peel and seed extracts, however, both had the strongest antiradical activity compared to the pulp. This study suggested that quince fruit and jam were a rich and inexpensive source of antioxidants, which could play a role in the prevention of free-radical-related chronic diseases. The antioxidant activity was attributed primarily to the presence of phenolic compounds.

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Silva, B.M., Andrade, P.B., Martins, R.C., Valentao, P., Ferreres, F., Seabra, R.M., and Ferreira, M.A., Quince (*Cydonia oblonga* Miller) fruit characterization using



Compound	3	6	8	3'
Quercetin 3-galactoside	O-Galactose	H	H	OH
Rutin	O-Rutinoside	H	H	OH
Kaempferol 3-glucoside	O-Glucose	H	H	H
Kaempferol 3-rutinoside	O-Rutinoside	H	H	H
Vicenin-2	H	Glucose	Glucose	H
Isoschaftoside	H	Arabinose	Glucose	H
Schaftoside	H	Glucose	Arabinose	H
Lucenin-2	H	Glucose	Glucose	OH
Stellarin-2	H	Glucose	Glucose	OCH ₃
6-C-pentosyl-8-C-glucoside of chrysoeriol	H	Pentose	Glucose	OCH ₃
6-C-glucosyl-8-C-pentoside of chrysoeriol	H	Glucose	Pentose	OCH ₃

SCHEME Q.50 Phenolic compounds of quince fruit and jam. (From Silva et

al., *J. Agric. Food Chem.*, 52:4705–4712, 2004. With permission.)

principal component analysis, *J. Agric. Food Chem.*, 53:111–122, 2005.

Silva, B.C., Andrade, P.B., Valentao, P., Ferreres, F., Seabra, R.M., and Ferreira, M.A., Quince (*Cydonia oblonga* Miller) fruit (pulp, peel, and seed) and jam: Antioxidant activity, *J. Agric. Food Chem.*, 52:4705–4712, 2004.

Quinoa

Quinoa (*Chenopodium quinoa*) is a hardy and nutritious Latin American pseudocereal (Ahamed et al., 1998). The seeds contain 15.6 percent crude protein, 7.7 percent fat, 69.5 percent carbohydrate, and 2.5 percent crude fiber (Chauhan et al., 1993). It has a high proportion of D-xylose (120.0 mg/100 g sample) and maltose (101.0 mg/100 g sample), and a low content of glucose (19.0 mg/100 g sample) and fructose (19.6 mg/g sample) (Ogungbenle, 2003). In general, the content of essential amino acids in quinoa is higher than in common cereals. Animal experiments showed NPU values of 75.7 and a biological value of 82.6 for the protein in raw quinoa. *In vitro* enzymatic methods showed that the digestibility of protein in quinoa was comparable to other high-quality food proteins (Chauhan et al., 1999; Ruales and Nair, 1992).

At least 16 saponins were detected in the seeds of *Chenopodium quinoa* exhibiting anti-fungal activity against *Candida albicans* and hemolytic activity on erythrocytes (Woldemichael and Wink, 2001). Estrada and coworkers (1998) reported earlier that saponins extracted from quinoa enhanced both systemic and mucosal antigen-specific antibody (IgG and IgA) responses in mice following intragastric or intranasal immunization with cholera toxin or ovalbumin. By increasing the permeability of the membrane, the quinoa saponins allowed a greater uptake of the antigen, making them a valuable adjuvant for generating systemic and mucosal responses.

Studies on minor cereals and pseudocereals without celiac activity, to meet the needs of individuals affected by celiac disease, showed the glycemic index (GI) for quinoa was slightly lower than that of gluten-free (GF) pasta and bread. In addition, quinoa induced lower free fatty-acid levels than GF pasta, and significantly lower triglyceride concentrations compared to GF bread. Thus, quinoa was a potential alternative to traditional foods demonstrating hypoglycemic effects (Berti, 2004).

Dini et al. (2004) identified a number of polyphenols in *Kancolla*, a sweet variety of *Chenopodium quinoa*. Five kaempferol and quercetin glycosides, as well as a glucoside of vanillic acid, were reported. Zhu and coworkers (2001) identified five ecdysteroids in quinoa seeds for the first time. These phytoecdysteroids were shown by Miller et al. (1985) to inhibit hypercholesterolemia and hyperglyceridemia in rats.

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R

Radish (*Raphanus sativus*)

Unlike the West, where the radishes are small-rooted vegetables, the Far East grows them as large-rooted vegetables (Curtis, 2003). They are cultivated for their fleshy, pungent, edible roots, which are usually reddish but sometimes white or black. The leaves and roots have been used in various parts of the world to treat cancer or as antimicrobial, antifungal, and antiviral agents (Terras et al., 1993; Gutierrez and Perez, 2004). Isothiocyanates present as thioglucoside conjugates in radish were shown to inhibit the development of tumors in many experimental models investigated (Conaway et al., 2002). Radishes are recognized as a food remedy for stones, gravel, and scorbutic conditions. The juice has been used for treating gall stones (choleithiasis) and for preventing the formation of biliary calculi. Kumar (2004) showed a diet containing radishes increased excretion of calcium oxalate compared to a self-selected diet, with the crystal count significantly higher in both genders.

Glucoraphanin, the natural precursor of sulforaphane found mostly in cruciferous vegetables, but also in radishes, is known for maintaining good health (West et al., 2004).

Using the bleomycin-Fe(III) method, the methanolic extract from radish sprouts (*Raphanus sativus*) was shown by Takaya et al. (2003) to be the most potent hydroxyl-radical scavenger of 11 commonly used vegetables, with close to double that of L-ascorbic acid (Figure R.86). This activity was attributed to the presence of various sinapic acid esters and flavonoids.

Matsufuji et al. (2003) attempted to isolate and characterize the reaction products of 12 acylated anthocyanins from red radish (*Raphanus sativus*) by reacting with 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) to generate peroxy radicals. A number of products were isolated, and their chemical structures determined by preparative HPLC to be *p*-hydroxybenzoic acid, 6-*O*-(*E*)-*p*-coumaroyl-2-*O*- β -D-glucopyranosyl- α -D-glucopyranoside,

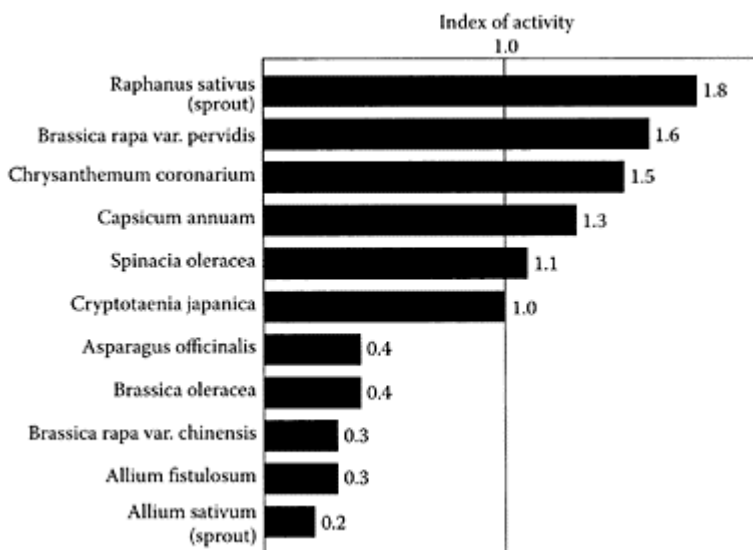


FIGURE R.86 Antioxidant activity of vegetables expressed as index of activity compared to ascorbic acid (1.0). (From Takaya et al., *J. Agric. Food Chem.*, 51:8061–8066, 2003. With permission.)

p-coumaric acid, 6-O-(E)-feruloyl-2-O- β -D-glucopyranosyl- α -D-glucopyranoside, and ferulic acid.

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Rapeseed

see also Canola Rapeseed, known scientifically as *Brassica napus* or *Brassica rapa*, is cultivated in northern climates primarily for animal feed and vegetable oil for human consumption and for biodiesel. According to the USDA, rapeseed is the third leading source of vegetable oil in the world in 2000 after soy and palm. Canola, a specific variety of rapeseed bred to have a low erucic-acid content (2.0 percent) in the oil and a low glucosinolate content (<18 mmol/g) in the meal, is grown in Canada, with related varieties grown in Europe. Barrett et al. (1998) showed that cruciferous seed meals that include rapeseed exerted protective effects against tumor formation and growth. Four potent, angiotensin-converting, enzyme-inhibitory peptides were isolated by Marczak et al. (2003) from subtilisin digestion of rapeseed protein. They lowered blood pressure in spontaneously hypertensive rats, suggesting the digest may be a promising functional food for preventing and treating hypertension. Del Mar Yust et al. (2004) recently treated rapeseed protein hydrolysates with the food-grade endoprotease, alcalase, and identified two fractions rich in HIV-protease inhibitors.

Thiyam et al. (2004) recently examined the antioxidant potential of rapeseed oil by-products and found the meal contained significant amounts of phenolic compounds. Of these, the major one was sinapic acid, and in the form of its esters and glucosides. These antioxidants could make a significant contribution to the meal industry.

The genotoxin potential of rapeseed oil cooking fumes was studied by Chen et al. (1992). The cooking fumes contained mutagenic activity, suggesting Chinese women exposed to such fumes were at high risk for lung cancer. However, it should be pointed out that the rapeseed grown in China is high in glucosinolates, resulting in much higher levels of sulfur in the oil and not characteristic of canola oil. In addition, many of the homes are poorly ventilated.

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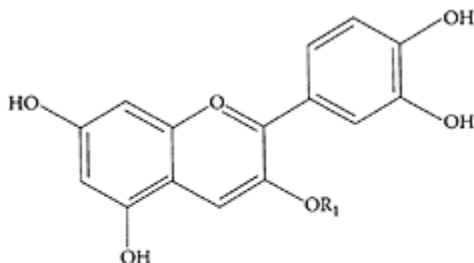
Raspberry (*Rubus idaeus*)

Raspberry is an aggregate fruit that is fleshy and contains seeds. It grows best in climates with cool summers and mild winters (Duel, 1996). Ethanol extracts from raspberry fruits showed *in vitro* anticancer activity on cervical- and breast-cancer cell lines (Wedge, 2001). Haung and coworkers (2002) proposed that the ability of black raspberries to inhibit the development of chemically induced esophageal and colon cancer in rodents and to inhibit benzo(a)pyrene-induced cell transformation *in vitro* may be mediated by impairing signal-transduction pathways, leading to activation of AP-1 and NF- κ B, known to be involved in tumor promotion/progression.

The fruits and leaves from red raspberry (*Rubus idaeus* L.) and black raspberry (*Rubus occidentalis* L.) plants were reported to be high in phenolics, with the highest antioxidant activity found at the ripe stage. Total anthocyanin content increased with maturity, with the leaves being higher in antioxidant activity than the fruits (Wang et al., 2000). The bright color of red raspberries is due to the presence of two anthocyanins, cyanidin-3-glucoside and cyanidin-3-sophoroside (Scheme R.51) (van Elbe and Schwartz, 1996).

Juranic and coworkers (2005) correlated the antiproliferative activity of the water extracts from the seed or pulp of five raspberry cultivars on malignant human colon carcinoma LSI74 cells with ellagic acid content.

Raspberry leaves are also high in tannins and, like its relative the blackberry, may relieve acute diarrhea (Tyler, 1994). The antimicrobial properties of raspberry juice, raspberry-leaf extract, and a commercial brand of raspberyleaf tea were investigated against five human pathogenic bacteria and two fungi. Raspberry juice was found to significantly reduce the growth of several species of bacteria, including *Salmonella*, *Shigella*, and *E. coli*. No antimicrobial activity was detected in the leaf extract or tea (Ryan et al., 2001). Lin et al. (2005) recently demonstrated the potential of enriching



Cyanidin-3-glucoside (R_1 = glucose)

Cyanidin-3-sophoroside (R_1 = sophoroside)

SCHEME R.51 Anthocyanins of red raspberry. (From Suthanthangjai et al., 2005)

wine or vodka with phenolics to inhibit *H. pylori* in laboratory medium. Raspberry-, cinnamon-, and peppermint-enriched wines all exhibited high antimicrobial activity, while raspberry-enriched vodka proved the most potent inhibitor of *H. pylori*.

Tea made from the leaves of *Rubus idaeus* L. (raspberry) has been used for centuries as a uterine relaxant in folk medicine. Rojas-Vera et al. (2002) reported that methanol extracts of dried raspberry have relaxant activity on transmurally stimulated guinea-pig ileum. Many women consume the raspberry leaf herb during their pregnancy, believing that it shortens labor and makes labor “easier.” Simpson and coworkers (2001) undertook a double-blind, randomized, placebo-controlled trial with 192 low-risk women who birthed their babies between May 1999 and February 2000. Raspberry leaf, consumed in tablet (2×1.2 g per day) from 32 gestation week until labor, was found to cause no adverse effects for mother or baby, but contrary to popular belief, did not shorten the first stage of labor. The only clinically significant findings were a shortening of the second stage of labor (mean difference=9.59 minutes) and a lower rate of forceps deliveries between the treatment group and the control group (19.3 percent vs. 30.4 percent) (Wang and Lin, 2000).

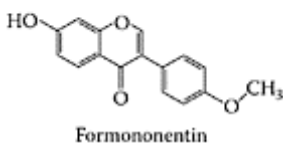
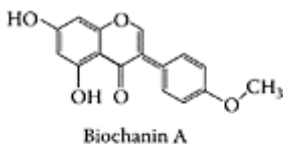
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Red clover

Red clover is a perennial herb that commonly grows wild in meadows throughout Europe and Asia, and has now been naturalized to grow in North America. The red flowers at the end of the branched stems are considered to be the source of its medicinal properties and are usually dried for therapeutic use. Red-clover (*Trifolium pratense*) extracts are becoming increasingly popular, primarily for the treatment of menopausal symptoms (Fugh-Berman and Kronenberg, 2001). Although promoted as a phytoestrogen source similar to soybeans, red clover is a medicinal herb, not a food, and traditionally has not been used for long term. Formononetin and biochanin A are the principal isoflavones of red clover, and are known to help



(Adapted from Hurr and Rafii, *FEMS Microbiol Lett.* 192:21–25, 2000.)

with hot flushes, which are a common menopausal complaint. The conflicting data on randomized, controlled trials of red clover for the control of menopausal symptoms are encouraging and suggest that phytoestrogens are a treatment modality that needs pursuing (Pitkin, 2004; Barentsen, 2004).

Current research has focused on a red-clover extract high in isoflavones as a possible treatment for symptoms associated also with cardiovascular health. Isolated isoflavones from red clover enriched in biochanin lowered LDL-C in men (Nestel et al., 2004). Campbell and coworkers (2004) recently reported that one-month supplementation with red clover isoflavones had a positive effect on HDL cholesterol. Mean daytime systolic and diastolic blood pressures were significantly lowered during isoflavone therapy,

compared to placebo, and forearm vascular endothelial function was significantly greater during isoflavone than placebo supplementation in postmenopausal, type 2 diabetic women. These data suggest that isoflavone supplementation from red clover may favorably influence blood pressure and endothelial function in postmenopausal, type 2 diabetic women (Howes et al., 2003).

Various studies also suggest that red-clover isoflavones may help prevent cancer. Jarred and coworkers (2003) found red-clover-derived isoflavones had a significant effect on prostatic growth, reducing the enlarged, nonmalignant prostate phenotype of the adult aromatase knock-out mouse, by acting as antiandrogenic agents rather than weak, estrogenic substances. Isoflavones in red clover significantly reduced the synthesis of prostaglandin E2 and thromboxane B2 ($p < 0.001$ to $p < 0.05$) in the murine macrophage cell line, indicating COX inhibition. Thus, it is possible that the lower rate of some cancers in populations with a high intake of dietary isoflavones may be linked to their inhibition of COX activity. In mice fed a diet supplemented with red-clover isoflavones, the prostatic epithelium displayed a significant increase in the production of estrogen-receptor beta and the adhesion protein E-cadherin, but a decrease in transforming growth factor beta. This study suggested that red-clover isoflavones represent a nontoxic dietary treatment for prostatic hyperplasia, reducing the potential for neoplastic transformation (Slater et al., 2002).

The activity of alkaline phosphatase increased following incubation of osteosarcoma cells (HOS58) with red-clover-chloroform extracts, suggesting a role for red-clover isoflavonoids in the stimulation of osteoblastic-cell activity.

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Red wines

see also Wines Polyphenols, mainly flavonoids, exert protective effects on the cardiovascular system (Wollin and Jones, 2001), as well as exhibit anticancer (Bianchini and Vainio, 2003), antiviral, and antiallergic properties (Bhat et al., 2001). In coronary heart disease, the protective effects of flavonoids are antithrombic, antioxidant, antiischemic, and vasorelaxant properties (de Lorimier, 2000). It has been hypothesized that the phenomenon of a low incidence of coronary heart disease in French people may be partially related to the pharmacological properties of polyphenolic compounds included in red wine (Zenebe and Pechanova, 2002). The mechanisms underlying CHD protective benefits of red wine have not been elucidated. Recently, the polyphenol resveratrol (*3,5,4'-trihydroxy-trans-stilbene*), known to be abundantly present in red wine compared to white wine, beer, or spirits, has been demonstrated to elicit a broad spectrum of biological responses in *in vitro* and in animal studies, including effects that are compatible with the cardioprotective roles proposed for red wine. Other studies relate exposure to wine/resveratrol with reduction in myocardial damage during ischemia-reperfusion, modulation of vascular cell functions (Wu et al., 2001), inhibition of LDL oxidation, and suppression of platelet aggregation (Halpern et al., 1998; Wu et al., 2001; Wollin and Jones, 2001). Grapes contain a variety of antioxidants, including resveratrol, catechin, epicatechin, and proanthocyanidins. Of these, resveratrol is present mainly in grape skin, while proanthocyanidin is present in the seeds. Das and coworkers (1999) demonstrated that red-wine extract, as well as resveratrol and proanthocyanidins, are equally effective in reducing myocardial ischemic reperfusion injury, which suggests that these redwine polyphenolic antioxidants play a crucial role in cardioprotection.

Schafer and Bauersachs (2002) reported that red wine may beneficially affect the development of high-altitude pulmonary edema, which is the predominant cause of death due to highaltitude illness. Two cellular mechanisms have been described for the altitude-related reduction in barometric pressure: enhanced endothelin 1 production and the increased generation of reactive-oxygen species. Both were suppressed by red wine.

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Rehmannia

Rehmannia refers to the root of *Rehmannia glutinosa*, an herb of the Scrophulariaceae family. The species name *glutinosa*



comes from glutinous, referring to the sticky nature of the root. Another name for rehmannia is Chinese foxglove.

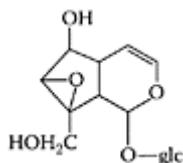
Rehmannia is a Chinese herb that is often combined with other herbs to treat anemia (Yuan et al., 1998; Zee-Cheng, 1992), cancer (Wei and Ru, 1997; Kamei et al., 2000), constipation, and diabetes. It has been mainly used to treat broken bones and severed sinews from falls. Oh and coworkers (2003) reported recently that *Rehmannia glutinosa* Libosch extracts stimulate the proliferation and activities of osteoblasts, while inhibiting the generation and resorptive activities of osteoclasts. It also shows preventive effects on osteoporotic bone loss induced by an ovariectomy. Other uses include the treatment of fatigue (Zee-Cheng, 1992) and high blood pressure (Yi et al., 1965). *Rehmannia* may be applied to the skin to treat eczema or psoriasis (Prieto et al., 2003) and may be beneficial

in the regulation of immediate-type allergic reaction (Kim et al., 1998). It may also be used to treat cuts and wounds (Luo, 1993).

In modern times, rehmannia is especially used for treating hormonal disorders, such as menopause, thyroid imbalance, and adrenal insufficiency (Shan, 1994; Chao et al., 2003).

The main components of rehmannia are simple sugars (including glucose, galactose, fructose, sucrose, and mannitol), which make the root sticky and give it the sweet taste. About half the content of dried rehmannia is stachyose and verbascone, polysaccharides that are difficult to digest. The stachyose extract from *Rehmannia glutinosa* Libosch had a significant, hypoglycemic effect in glucose- and adrenaline-induced hyperglycemic and alloxan-induced diabetic rats (Zhang et al., 2004).

The major active constituents of rehmannia are iridoid glycosides. In a study of several samples of rehmannia, Luo et al. (1994) found that catalpol made up about 3–11 percent of the undried root content. The pharmacological action of catalpol and related iridoids involved



Catalpol. (Adapted from Li et al., *Brain Res.*, 1029:179–185, 2004.)

production of adrenal cortical hormones (HsonMou and Pui-Hay, 1986). These hormones have anti-inflammatory action (explaining the claimed benefits of rehmannia for asthma, skin diseases, and arthritis) and are also involved in the production of sex hormones (explaining the claimed benefit of treating menopause, impotence, and other signs of hormone deficiency). Recent research by Li et al. (2004) suggested catalpol were a potential neuroprotective agent, and its neuroprotective effects were achieved, at least partly, by promoting endogenous anti-oxidant enzymatic activities and reducing the formation of nitric oxide. Kim and coworkers (1999) suggested rehmannia may inhibit TNF- α secretion by inhibiting IL-1 secretion and has an anti-inflammatory activity in the central nervous system, curing some pathological-disease states.

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Resistant starch

Resistant starch is starch that resists digestion by enzymes in the small intestine. It is found naturally in many cereals and grains, as well as in some processed foods, such as extruded cereals (Brown, 2004). Resistant starch functions like a fiber in the diet, as it plays a role in gut health (Asp et al., 1996). In humans, resistant starch lowers fecal bileacid excretion (Langkilde et al., 1998). In their review, Young and Leu (2004) showed that the consumption of resistant starch dramatically affected the colonic luminal environment by facilitating apoptotic deletion of genetically damaged cells in the colon, several of which are considered to be biomarkers associated with risk for colorectal

cancer. In addition, its ability to lower colonic pH is usually considered beneficial for cancer prevention, as well for mineral bioavailability in the colon (Champ, 2004). Cheng and Lai (2000) showed that resistant rice starch was fermented to produce propionic acid, which resulted in reduction in serum total cholesterol, serum LDL cholesterol, hepatic cholesterol, and hepatic triglycerides in rats. Foods in this class also have a low glycemic index and reduce postprandial-insulin levels and increase HDL cholesterol levels (Kendall et al., 2004; Park et al., 2004). Other researchers found that retrograded resistant starch was a very potent butyrate producer (Bird et al., 2000; Topping and Bird, 1999). In a recent review, Brouns and coworkers (2002) highly recommend resistant starch in relation to butyrate. Higgins et al. (2004) reported that replacement of 5.4 percent of the total dietary carbohydrate with resistant starch increased postprandial lipid oxidation significantly and therefore might decrease fat accumulation in the long term.

The protective effect of high-amylose cornstarch ingestion on trinitrobenzene sulfonic acid-induced colitis suggested to Morita et al. (2004) that it altered the colonic mucosa, possibly due to the production of cecal short-chain fatty acids.

In summary, resistant-starch intake seems to decrease postprandial glycemic and insulinemic responses, lower plasma cholesterol and triglyceride concentrations, improve whole-body insulin sensitivity, increase satiety, and reduce fat storage. These properties make resistant starch an attractive dietary target for the prevention of diseases associated with dyslipidemia and insulin resistance, as well as the development of weight-loss diets and dietary therapies for the treatment of type 2 diabetes and coronary heart disease (Higgins, 2004).

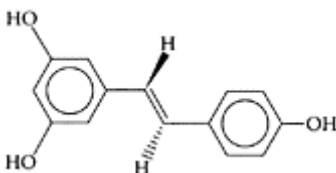
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Resveratrol

Resveratrol is a trihydroxystilbene in the skins of grapes and in wine. It is a powerful phytoestrogen with a wide range of pharmacological and therapeutic health benefits. The beneficial effects of wine on cardiovascular health include prevention of oxidative



Resveratrol. (From Li et al., *Free Rad. Biol. Med.*, 38:243–257, 2005. With permission.)

damage, vasodilation, and prevention of platelet aggregation. Laden and Porter (2001) showed it was resveratrol that inhibited purified human squalene monooxygenase, a rate-limiting enzyme in cholesterol biosynthesis. Thus, protection by resveratrol is related to inhibition of cholesterol synthesis. Other mechanisms for the protection of the cardiovascular system by resveratrol include defense against ischemic-reperfusion injury, promotion of vasorelaxation, protection and maintenance of intact endothelium, antiatherosclerotic properties, inhibition of low-density lipoprotein oxidation, suppression of platelet aggregation, and estrogen-like actions (Hao and He, 2004). Gusman and coworkers (2001) reappraised the chemopreventive and chemotherapeutic properties of resveratrol. The literature confirmed the ability of resveratrol to inhibit activation of carcinogenic compounds, stimulate detoxification, prevent interaction with DNA, and, finally, to suppress tumor progression (Teel and Huynh, 1998). Bhat and Pezzuto (2001) reported that resveratrol exerted antiproliferative effects in cultured human endometrial adenocarcinoma (Ishikawa) cells involving either both estrogen-dependent and estrogen-independent mechanisms. Resveratrol has been shown to significantly alter the cellular physiology of tumor cells, as well as block initial and progression of the tumors. Zoberi et al. (2002) showed that resveratrol altered both cell-cycle progression and cytotoxic response to ionizing radiation in two cervical

TABLE R.60
Mechanisms of Resveratrol in Cells *In Vitro*
Related to Cancer Chemoprevention

Mechanism	Experimental system	“Efficacious” concentrations (μM)^a
Inhibition of growth	Multiple cell lines	~5–10
Induction of apoptosis	Leukemia cells	32–100
Induction of p53-independent apoptosis	Colon tumor cells	100
Estrogen agonism	Mammary cells	10–25
Antiestrogenicity	Mammary cells	0.1–1
Inhibition of oxygen radical formation nitric oxide production	Macrophages	~30
Inhibition of cytochrome P450 enzymes: CYP1A1 CYP1B1, CYP3A4	Liver cells, microsomes, recombinant enzyme	1–20
Activation of p53	Mouse epidermal cells	20
Activation of c-jun kinase	Mouse epidermal cells	10–40
Decrease in COX-2 expression	Mammary epithelial cells	~5
Increase in p21/Cipl, cyclins D1, D2, E; decrease in cdks 2,4,6	Epidermoid carcinoma cells	~10
Increase in cyclins A, B1, and cdks 1 and 2	Colon tumor cells	30
Inhibition of protein kinase C activity	Gastric cells	50
Inhibition of protein kinase D activity	Fibroblasts	>100
Inhibition of NF-κB ^b activation	Monocytes, macrophages	30
Inhibition of NF-κB and AP-1 activation	Myeloid, lymphoid, epithelial cells	5

^a Lowest concentrations at which reproducible changes have been observed, or IC₅₀ or EC₅₀, if provided.

^b NF-κB, nuclear factor κB.

Source: From Gescher and Steward, *Cancer Epidemiol. Biomarkers Prev.*, 12:953–957, 2003. With permission.

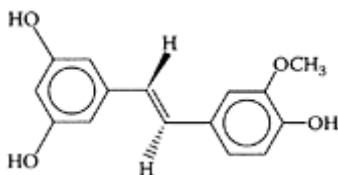
tumor cell lines. Resveratrol was also shown by Niles and coworkers (2003) to inhibit growth and induce apoptosis in two human melanoma-cell lines. Thus, resveratrol could be effective as a therapeutic or chemopreventive agent against melanoma.

Pharmacokinetic studies revealed that the target organs of resveratrol are liver and kidney, where it is concentrated after absorption, and is mainly converted to a sulfated

form and a glucuronide conjugate. *In vivo*, resveratrol blocks the multistep process of carcinogenesis at various stages: it blocks carcinogen activation by inhibiting aryl hydrocarbon-induced CYP1A1 expression and activity, and suppresses tumor initiation, promotion, and progression. Besides chemopreventive effects, resveratrol appears to exhibit therapeutic effects against cancer (Aggarwal et al., 2004). Kundu and Surh (2004) reviewed the molecular mechanisms underlying chemoprevention by resveratrol, with special focus on its effect on cellular-signaling cascades mediated by NF- κ B and AP-1. The various mechanisms associated with cancer prevention by resveratrol are listed in Table R.60.

Mertens-Talcott and Percival (2005) recently reported that ellagic acid and quercetin both interacted synergistically with resveratrol, inducing apoptosis and causing transient cell-cycle arrest in human leukemia cells (MOLT-4).

Liu and Liu (2004) showed both resveratrol and its analogue, isorhapontigenin, inhibited oxidation of LDL and the generation of reactive-oxygen species. Li and coworkers (2005) recently reported that isorhapontigenin prevented cardiac hypertrophy, a major cause of morbidity and



Isorhapontigenin. (From Li et al., *Free Rad. Biol. Med.*, 38:243–257, 2005. With permission.)

mortality worldwide. As an antioxidant, the mechanism involved inhibition of intracellular signaling transduction pathways.

The ability of resveratrol to protect against age-related macular degeneration (AMD) was recently demonstrated by King et al. (2005), who showed resveratrol significantly reduced cell proliferation of a human retinal epithelium cell line (ARPE-19). At a concentration of 100 μ mol/L, resveratrol inhibited H₂O₂-induced intracellular oxidation and protected retinal pigment epithelium from H₂O₂-induced cell death.

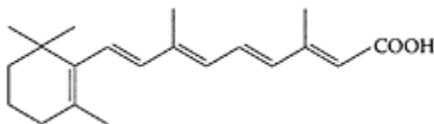
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Retinoic acid

see also Retinol and Vitamin A Retinoic acid (RA), a transcriptionally active metabolite of vitamin A (retinol), activates two families of nuclear-retinoid receptors that have the potential to regulate the expression of a



All-trans-retinoic acid (RA). (From Seo et al., *Eur. J. Pharm. Biopharm.*, 58:681–687, 2004. With permission.)

large number of genes (Soprano et al., 2004). Retinoids are essential for normal embryo development and epithelial differentiation (Klug et al., 1989; Gajovic et al., 1998). These

compounds are also involved in chemoprevention and differentiation therapy of some cancers (Hayashi et al., 2000; Yang et al., 2002), with particularly impressive results in the management of acute promyelocytic leukemia (Otsuki et al., 2004; Avvisati and Tallman, 2003). RA is derived from retinol by oxidation through retinol and retinal dehydrogenases, and several cytochrome P450S. The mechanisms that serve to adjust the metabolism of vitamin A to maintain retinoid homeostasis and prevent retinoid excess are not well understood, but the diet has some effects (Ross, 2003).

Maden and Hind (2004) have shown that RA is also required during alveologenesis and throughout life for the maintenance of lung alveoli. When rats are deprived of dietary retinol they lose alveoli and show the features of emphysema.

Ping and coworkers (2005) recently examined the effect of all-*trans*-retinoic acid on p62, a tumor-associated autoantigen identified with autoantibodies from patients with hepatocellular carcinoma (Zhang et al., 1999). RA induced apoptosis in a human gastric cancer-cell line BGC-823 by downregulation and translocation of p62.

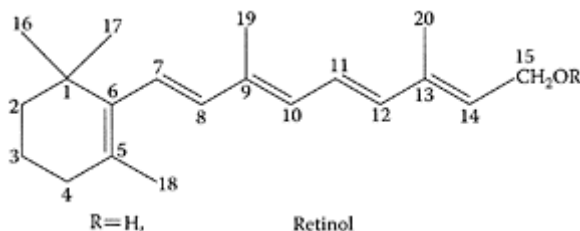
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Retinol

see also Retinoic acid, Vitamin A Retinol, the alcohol form of vitamin A, is stored as retinyl esters and delivered from liver stores into the bloodstream as retinol bound to a retinol-binding protein. In situations of high vitamin A demand (e.g., inflammation, diseases, prenatal period), this supply can be insufficient because of delayed production of retinol-binding protein, leading to local deficiencies and impairment of structure and function in the respective tissues. This delay may be overcome by cellular-retinyl esters stores that can be enriched by topically applied retinyl esters (Biesalski and Nohr, 2004).

The metabolism of vitamin A (retinol) to retinyl esters by lecithin:retinol acyl-transferase has been found to be substantially reduced in human carcinoma cell lines. Recently, Boorjian and coworkers (2004) tested normal and malignant bladder-tissue specimens from human patients and found a significant reduction in lecithin: retinol acyl-transferase expression in bladder cancer with an inverse correlation between lecithin:retinol acyl-transferase mRNA and protein expression with increasing



Retinol structure. (From Choi et al., *Anal. Chim. Acta*, 512:141–147, 2004. With permission.)

tumor stage. These data suggest that loss of lecithin:retinol acyl-transferase expression is associated with invasive bladder cancer.

The all *trans* form of retinol is a naturally occurring form, which can be converted to a corresponding geometrical isomer, 9-*cis*-retinol form. In fact, 9-*cis*-retinol in combination with *cis*-retinol dehydrogenase was found to inhibit breast-cancer cell proliferation by producing retinol metabolites other than 9-*cis*-retinoic acid (Paik et al., 2005). An epidemiological study on postmenopausal women in Sweden revealed that chronic excess of retinol intake (> 1.5 mg/day) decreased bone-mineral density and increased hip-fracture risk (Whiting and Lemke, 1999). Skeletal effects of toxic amounts of vitamin A are known from acute toxic exposure to chronic high-dose intake of vitamin A. Such effects have led experts to speculate that long-term consumption of diets high in vitamin A (retinol) that stimulate bone resorption and inhibit bone formation may contribute to osteoporosis and hip fractures (Genaro Pde and Martini, 2004; Boucher et al., 2003).

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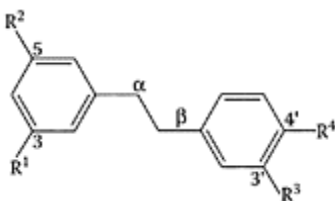
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Rhubarb

The rhubarb plant originated in Tibet or Mongolia, and from the 16th to 18th centuries was used medicinally in Europe and Asia. It served as a laxative, antiphlogistic, and



Red rhubarb stalks.



Compound	a-b	R ¹	R ²	R ³	R ⁴
Piceatannol	C=C	OH	OH	OH	OH
3,5,4'-Trimethylpiceatannol	C=C	OCH ₃	OCH ₃	OH	OCH ₃
Trimethylresveratrol	C=C	OCH ₃	OCH ₃	H	OCH ₃

SCHEME R.52 Stilbene structures. (Adapted from Matsuda et al., *Bioorg. Med. Chem.*, 12:871–4876, 2004.)

homeostatic in the treatment of constipation, diarrhea, jaundice, gastrointestinal hemorrhage, menstrual disorders, conjunctivitis, traumatic injuries, superficial supportive suppurative sores, and ulcers (Peigen et al., 1984; Gu et al., 2000). Chunsheng et al. (2000) suggested rhubarb can ameliorate acute lung injury by inhibiting intercellular adhesion molecule mRNA expression. It can also be applied externally for thermal burns. Chen et al. (2001) reported that rhubarb reduced intestinal juice IgA content in mice caused by burn, which suggested an important mechanism of rhubarb was involved in protecting the muco-membranous barrier.

The edible stalk, about an inch wide, is often more than a foot long and is composed of 95 percent water. It is a fair source of potassium, contributing minor amounts of vitamins, and is low in sodium. Rhubarb's crisp, sour stalks are rich in vitamin C, dietary fiber, and calcium, although the calcium is combined with oxalic acid. Oxalic acid can lead to an increase in urinary-oxalate excretion, which is a risk factor for kidney-stone formation. Rhubarb is somewhat acidic (pH 3.1–3.2), with one cup of diced rhubarb containing about 26 calories.

Stilbenes were isolated from Korean rhubarb by Matsuda et al. (2004) and their antiallergic activities studied *in vitro*. Their results revealed that 3,5,4'-trimethylpiceatannol exhibited the most potent inhibition against β -hexosaminidase release as a marker of degranulation, followed by trimethylresveratrol (Scheme R.52). Piceatannol, 3,5,4'-trimethylpiceatannol, resveratrol, and trimethylresveratrol all significantly inhibited antigen-induced release of TNF- α and IL-4.

Iizuka et al. (2004) attempted to estimate the antioxidative activity of rhubarb components on low-density lipoprotein (LDL). They reported a significant, multiple correlation coefficient for antioxidative activities on LDL ($R=0.914$, $p<0.01$) involving five components: aloe-emodin, chrysophanol, emodin 1- O - β -D-glucoside, lindleyin, and 6-hydroxymusizin 8- O - β -D-glucoside.

Rhubarb was also reported to exert protective effects on severe acute pancreatitis, probably by inhibiting inflammation of the pancreas, improving pancreatic microcirculation, and altering exocrine secretion (Zhao et al., 2004). Emodin and rhein

isolated from rhubarb were found to be major iNOS inhibitors and may possibly serve as bioactive substances for anti-inflammation effects (Wang et al., 2002).

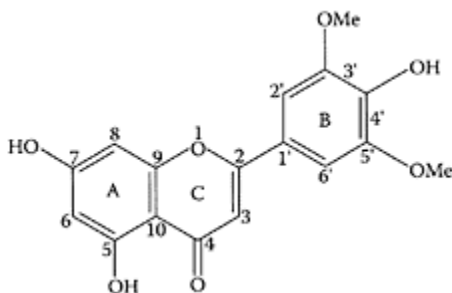
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Rice

Rice (*Oryzae sativum*) is the principal food crop in Asia, where the incidence of breast and colon cancer is markedly below that found in the Western world. Hudson et al. (2000) investigated the potential colon and breast tumor-suppressive properties of rice. Their results suggested that brown rice and bran contain compounds had putative cancer chemopreventive properties. The phenols exhibiting this activity were present in brown-rice bran, such as triclin (Cai et al., 2004). However, they are present at much lower levels in white compared to brown rice. Thus, the consumption of rice bran or brown rice instead of milled white rice may be advantageous with respect to cancer prevention.

While triclin was a potent inhibitor of breast tumor-cell growth *in vitro*, Cai et al. (2004) found it had little effect on nude mice bearing human-derived malignant MDA-MB-468 breast-



Cancertricin structure. (4',5,7-trihydroxy-3',5'-dimethoxy-flavone).
(From Cai et al., *Br. J. Cancer*, 91:1364–1371, 2004. With permission.)

tumor cells. However, the high levels of tricrin in the gastrointestinal tract after dietary intake may prove beneficial in preventing colorectal cancer.

Other investigations of potential beneficial effects of specific rice constituents in terms of prevention or amelioration of malignant disease have been published. These reports suggest that rice constituents counteract chemical-induced mutagenicity (Kang et al., 1996; Nam and Kang, 1997), tumor promotion (Yasukawa et al., 1998), carcinogenicity (Aoe et al., 1993), and established neoplastic growth in rodents (Hayashi et al., 1998; Koide et al., 1996). However, relatively little is known about which specific molecules may be responsible for these activities. Some of the evidence concerning the chemopreventive and antitumor properties of rice suggests that it is predominantly the bran portion of the grain that contains biologically active substances. The preventive potential of rice bran extract against the oxygen radical-related chronic diseases, such as cardiovascular diseases and cancer, antioxidative and antigenotoxic activities of the rice-bran extracts was demonstrated recently by Higashi-Okai et al. (2004).

Rice-bran oil is tenaciously believed to be a healthy vegetable oil in Asian countries. It exerts hypocholesterolemic activity in relation to more commonly used vegetable oils and is characterized by a relatively high content of nonfatty-acid components, some of which are known to have beneficial health effects, such as gamma-oryzanol and tocotrienols that could participate in its hypocholesterolemic effects (Sugano et al., 1999).

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Rice starch

Rice starch cannot be completely digested by enzymes in the small intestine. Cheng and Lai (2000) demonstrated that resistant rice starch is fermented to produce propionic acid, which reduced serum total cholesterol, serum LDL cholesterol, hepatic cholesterol, and hepatic triglyceride in rats. Kim et al. (2003) reported that resistant starch from rice could also shorten the intestinal transit time and could lower plasma total lipid and cholesterol concentrations compared to diabetic control.

Rice-starch-based oral rehydration solution (ORS) has been shown to be a suitable alternative to glucose-based ORS in the treatment of both cholera-genic and noncholera-genic dehydration in older infants and in children and also in the rehydration of acute diarrheal dehydration in infants below 6 months of age (Iyngkaran and Yadav, 1998).

Rice starch added to bath water was found to have beneficial effects on impaired barrier function, as evaluated by trans-epidermal water-loss measurements. Rice starch in powder or formulated in a bath product is therefore recommended by de Paepe et al. (2002) as a skin-repair bathing additive for barrier-damaged skin, particularly in the case of atopic dermatitis patients.

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Rooibos tea

Rooibos tea is an herbal tea produced from the leaves and fine stems of the South African leguminous shrub *Aspalathus linearis*, also known as Rooibos. The herbal tea is considered a health drink due to the presence of beneficial phenolic antioxidants. The antioxidant properties of Rooibos tea were found to be similar to green, oolong, and black tea (von Gadow et al., 1997a). Rooibos tea, however, contains a unique compound, aspalathin, that mimics superoxide dismutase (SOD) (Yoshikawa et al., 1990; Ito et al., 1991). Compared to BHA, BHT, and α -tocopherol, aspalathin exhibited the highest radical-scavenging activity (von Gadow et al., 1997b). *In vitro* and *in vivo* studies found rooibos tea exhibited anti-mutagenic properties against aflatoxin B₁ and 2-acetylaminofluorene-induced mutagenesis (Marnewick et al., 2000; Marnewick et al., 2004a). In addition, aqueous extracts of rooibos tea enhanced phase II detoxifying enzymes, glutathione-S transferase, and UDP-glucuronyl transferase in rat liver, stabilizing glutathione (GSH) (Marnewick et al., 2003). Ethanol/ acetone (E/A)-soluble fractions prepared from methanolic extracts of processed and unprocessed South African herbal teas, rooibos, and honeybush compared to green tea were recently shown by Marnewick and coworkers (2004b) to inhibit tumor promotion in mouse skin. Using the two-stage mouse-skin carcinogenesis assay with the tumor promoter 12-*O*-tetra decanoylphorbol-13-acetate (TPA) on ICR mouse skin initiated with 7,12-dimethyl benz[a]anthracene (DMBA), they found herbaltea fractions significantly ($p<0.001$) decreased tumor volume, as well as delayed their development (Figure R.87). Compared to the control, tumors did not appear in the DMBA/TPA-treated mice at 4 and 12 weeks when maintained on processed and unprocessed rooibos, respectively. Green tea exhibited 100 percent

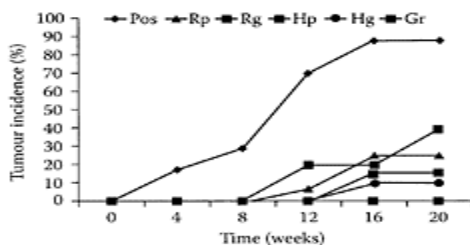
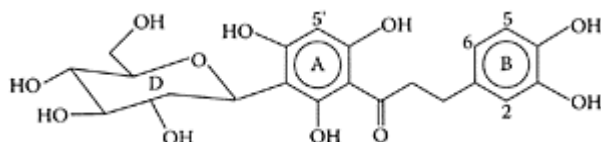


FIGURE R.87 Inhibitory effect of topical application of various E/A polyphenolic fractions on TPA-induced tumor promotion. The percentage of mice with tumors is plotted as a function of the treatment period (weeks). The fractions include Rp, processed rooibos; Rg, unprocessed rooibos; Hp, processed honeybush; Hg, unprocessed honeybush; and Gr, green tea. The number of animals per group=15–20. (From Marnewick et al., *Cancer Lett.*, 224:193–202, 2005.)

inhibition compared to 90 percent and 84.2 percent inhibition for unprocessed and processed honeybush. While processed and unprocessed rooibos proved to be the least effective, they nevertheless accounted for an impressive 75 percent and 60 percent inhibition of tumor promotion, respectively. The variability in tumor inhibition exhibited by these herbal teas was attributed to differences in their flavonol/proanthocyanidin and flavonol/flavone composition and nonpolyphenolic components.

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Aspalathin. (From Jaganyi and Wheeler, *Food Chem.*, 83:121–126, 2003. With permission.)

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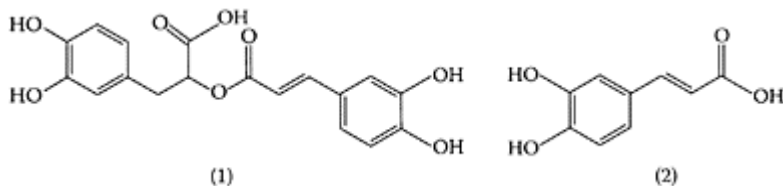
Rosemary

see also Rosmarinic acid Rosemary (*Rosmarinus officinalis* Linn.) is a common household plant. It is used as food flavoring and a beverage drink, as well as in cosmetics. In folk medicine, it is used as an antispasmodic in renal colic and dysmenorrhoea, to relieve respiratory disorders, to stimulate growth of hair, and as a mild analgesic and antimicrobial agent (Newall, 1996). Extract of rosemary relaxes smooth muscles of trachea and intestine, and has choleric, hepatoprotective, and antitumorigenic activity (Al-Sereiti et al., 1999). The leaves of rosemary contain valuable essential oils rich in mono- and sesquiterpenes, including borneol, camphor, carophyllene, cineol, humulene, linalool, and thujone “salviol.” The strong, antioxidant activity associated with rosemary leaves is associated with these phenolic diterpenes.

The most important constituents of rosemary are caffeic acid and its derivatives, such as rosmarinic acid. These compounds and other phenolic diterpenes, flavonoids, and phenolic acids (Ho et al., 2000) have antioxidant effects. Slamenova et al. (2002) also reported that rosemary extract exhibits a protective effect against oxidative damage to DNA as a consequence of scavenging of both OH radicals and singlet oxygen.

Rosmarinic acid, a caffeic-acid derivative, is well-absorbed from the gastrointestinal tract and from the skin. It increases the production of prostaglandin E2 and reduces the

production of leukotriene B₄ in human polymorphonuclear leucocytes, and inhibits the complement system (Al-Sereiti et al., 1999). It also showed therapeutic potential in treatment or prevention of bronchial asthma, spasmogenic disorders, peptic ulcer, inflammatory diseases, hepatotoxicity, atherosclerosis, ischaemic heart disease, cataract, cancer, and poor sperm motility (Rampart et al., 1986; Al-Sereiti et al., 1999).



Rosmarinic acid (1) and caffeic acid (2). (From Wang et al., *Food Chem.*, 87:307–311, 2004.)

Among the antioxidant compounds in rosemary leaves, ~90 percent of the antioxidant activity can be attributed to carnosol and carnosic acid. Topical application of rosemary extract, carnosol, or ursolic acid to mouse skin inhibited the covalent binding of benzo[a]pyrene to epidermal DNA, tumor initiation by 7,12-dimethylbenz[*a*]anthracene (DMBA), TPA-induced tumor promotion, ornithine decarboxylase activity, and inflammation (Huang et al., 1994).

Additional studies revealed that carnosic acid and carnosol strongly inhibited phase I enzyme CYP 450 activities and induced the expression of the phase II enzyme, glutathione S-transferase (GST) (Mace et al., 1998). These results give insight into different mechanisms involved in the chemopreventive actions of rosemary.

Recently Lo et al. (2002) demonstrated that carnosol can suppress the NO production and iNOS gene expression by inhibiting NF- κ B activation, and provide possible mechanisms for its anti-inflammatory and chemopreventive action.

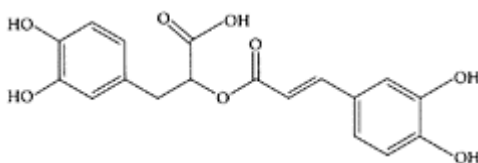
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Rosmarinic acid

see also Rosemary Rosmarinic acid is a phenolic compound widely distributed in *Labiatae* herbs, such as rosemary, sweet basil, and perilla (Scarpati and Oriente, 1958; Makino et al., 1998). This naturally occurring polyphenol exhibits antioxidant



Rosmarinic acid. (From Wang et al., *Food Chem.*, 87:307–311, 2004. With permission.)

(Tada et al., 1996) and anti-inflammatory effects, such as inhibitory effects on a complement-dependent inflammatory process (Peake et al., 1991), 5-lipoxygenase (Yamamoto et al., 1998), and histamine release from mast cells (Rimando et al., 1987). Sanbong et al. (2003) showed that it inhibited diesel-exhaust particles (DEP)-induced lung injury by reducing the expression of the macrophage inflammatory protein-1 α .

Toshiaki et al. (2000) reported rosmarinic acid inhibited cytokine-induced mesangial-cell proliferation and suppressed platelet-derived growth factor (PDGF) and c-myc mRNA expression in PDGF-stimulated mesangial cells, all of which suggest that it might be a promising agent to prevent mesangial-cell proliferation.

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Rosy or Madagascar periwinkle (Other names: Cape Periwinkle, *Catharanthus roseus*, Church Flower, Red Periwinkle)



Rosy periwinkle (*Catharanthus roseus*), a medicinal plant found on the island of Madagascar, was used in traditional medicines for the treatment of cancer, Hodgkin's disease, and leukemia in children (Cardinali, 1973). Synthetic vincristine, used to treat leukemia, is only 20 percent as effective as the natural product derived from *Catharanthus roseus*. It was also found to have some potent blood-sugar-lowering activity (Chattopadhyay, 1999). Wang et al. (2004) reported that aqueous extracts of *Catharanthus roseus* significantly inhibited proliferation of cultured bovine aortic endothelial cells at a concentration of 1 g dry herb/mL, suggesting its role as a potential antiangiogenic agent. However, the use of *Catharanthus roseus* is not recommended due to the risk of severe side effects (Carod-Artal, 2003). Chemicals derived from it are used in prescription-only anticancer drugs (Ram and Kumari, 2001). *Catharanthus roseus* and

the drugs derived from it have been associated with causing birth defects, neurotoxicity, bone-marrow suppression, and sensitivity to sunlight (Mathur and Chaudan, 1985). In addition, it may also cause gastrointestinal complaints, headache, and muscle weakness.

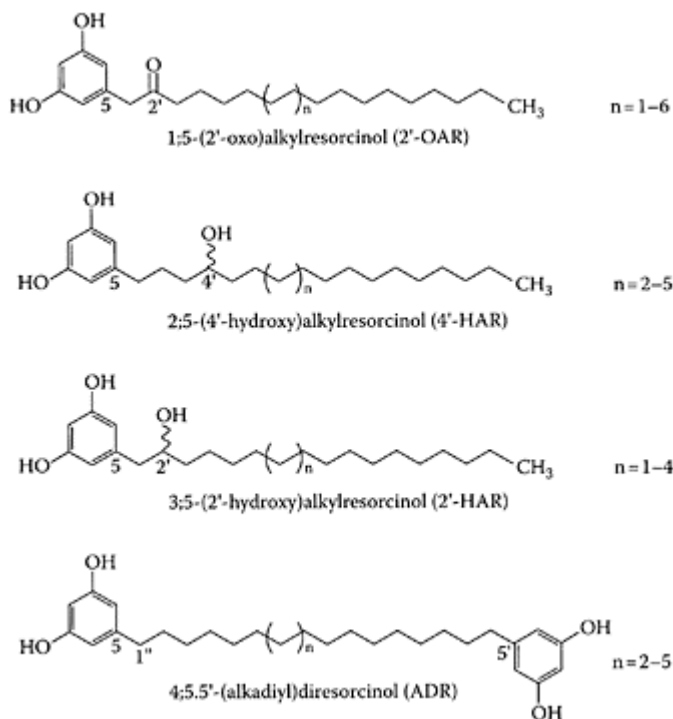
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Rye

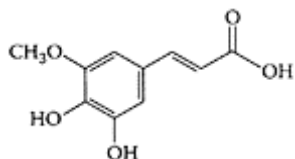
see also Ferulic acid Rye bran contains, in addition to a high-content dietary fiber, plant lignans and other bioactive compounds, such as alkylresorcinols (AR) (Ross et al., 2004). These are phenolic lipids present in large amounts in the bran fraction of rye (Scheme R.53). They are amphiphilic 1,3-dihydroxybenzene derivatives with an odd-numbered alkyl chain at position 5 in the benzene ring (Kozubek and Tyman, 1999). Early research reported serious growth inhibition and other pathological symptoms in several animal species (Sedlet et al., 1984). Other reports, however, suggest ARs have anti-bacterial and antifungal properties, as well as antiparasitic, antitumor, and antioxidant properties (Kozubek and Tyman, 1999). Gasiorowski and coworkers (1996) showed AR markedly decreased the mutagenic effects of a number of mutagens using the Ames test. Kamileldin and coworkers (2001) showed AR exhibited antioxidant activity *in vitro*, but it was still poor relative to α -tocopherol.

At present, evidence from studies in human subjects does not warrant the conclusion that rye, whole grains, or phytoestrogens protect against cancer. Some studies, however, have pointed in that direction, especially in relation to cancers of the upper digestive tract and of



SCHEME R.53 Skeletal structures of alkylresorcinol-related analogs in rye. (From Suzuki et al., *Phytochemistry*, 52:281–289, 1999. With permission.)

the colon (Grasten et al., 2000). Rye foods also improved bowel health, as assessed by relevant markers (McIntyre et al., 1993; McIntosh et al., 2003). In comparison to wheat, rye is a slightly better source of total dietary fiber and is more commonly used in whole-grain food forms, which, together with cellulose, contributes more mixed linked 1→3,1→4 β-glucan and arabinoxylan (Aman et al., 1997). The latter fiber types are of particular interest, because they are present in soluble and insoluble forms, and arabinoxylan is considered to be an optimal substrate for fermentative generation of short-chain fatty acids in particular, and of butyrate in the colon. High concentration of butyrate in the colon is hypothesized to improve bowel health and lower cancer risk by several possible mechanisms (Bach et al., 1997). Ferulic acid, the major phenolic compound in rye bran and an antioxidant *in vitro*, however, did not produce a measurable antioxidative effect on human LDL (Harder et al., 2004).



Ferulic acid. (Adapted from Hynes and O’Coinceanainn, *J. Inorg. Biochem.*, 98:1457–1464, 2004.)

A number of prospective epidemiological studies have clearly shown a protective effect by whole-grain cereals against myocardial infarctions (Pietinen et al., 1996). A corresponding protective effect against diabetes (Leinonen et al., 1999) and ischemic stroke (brain infarct) have also been demonstrated (Hallmans et al., 2003). A high-fiber rye diet decreased insulin secretion, measured as decreased excretion of C-peptide in the urine and decreased plasma insulin peaks at the end of the day, during nibbling regimen (Lundin et al., 2004).

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S

Saffron

see also Crocin Saffron (*Crocus sativus* L.) is an important spice grown in Greece, Spain, Turkey, Iran, India, and Morocco. In folklore medicine, as well as in modern pharmacy, saffron has been reputed to be useful in treating numerous human diseases, such as cardiovascular diseases (Grisolia, 1974; Abdullaev, 1993) and neurodegenerative disorders accompanying memory impairment (Abe and Saito, 2000). It contains three main, pharmacologically active metabolites: (1) saffron-colored compounds crocins, which are unusual, water-soluble carotenoids. The digentiobiosyl ester of crocetin— α -crocetin—is the major component of saffron. (2) Picrocrocetin is the main substance responsible for the bitter taste in saffron. (3) Safranal is the volatile oil responsible for the characteristic saffron odor and aroma. Furthermore, saffron contains proteins, sugars, vitamins, flavonoids, amino acids, mineral matter, gums, and other chemical compounds (Rios et al., 1996; Winterhalter and Straubirger, 1971.)

Studies by Escribano and coworkers (1996) found extracts from saffron inhibited cell growth of human tumor cells. Cells treated with crocin proved very effective in inhibiting tumor growth. A growing body of research has demonstrated that the saffron extract itself and its main constituents, the carotenoids, possess chemopreventive properties against cancer. A review by Abdullaev and Espinosa-Aguirre (2004) discusses the recent literature on the anticancer activities of saffron and its main ingredients.

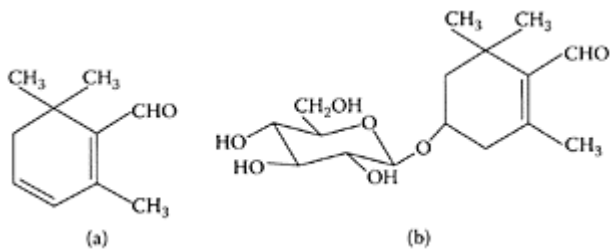
An earlier study by Xuan et al. (1999) on ischemic retinopathy and age-related macular degeneration found that monosaccharide analogues of crocin, because of their ability to significantly increase blood flow to the retina, could be used to alleviate this condition.

Crocetin was found to enhance oxygen diffusivity through liquids, such as the plasma. As a consequence of this property, crocetin has been observed to increase alveolar oxygen transport and to enhance pulmonary oxygenation. It improves cerebral oxygenation in hemorrhaged rats and acts positively in atherosclerosis and arthritis treatment (Giaccio, 2004).

A significant reduction in papilloma formation was found with saffron application in the preinitiation and postinitiation periods. The inhibition appeared to be partly due to the modulatory effects of saffron on some phase II detoxifying enzymes, such as glutathione *S*-transferase, glutathione peroxidase, catalase, and superoxide dismutase (Das et al., 2004).

In a double-blind, randomized clinical pilot trial, Noorbala et al. (2005) showed a hydroalcoholic extract from saffron was as effective as the drug fluoxetine in treating

mild to moderate depression (Figure S.88). Based on their results, a larger-scale trial was strongly recommended.



Saffranal (a) picrocrocin (b). (Adapted from Lozano et al., *J. Biochem. Biophys. Methods*, 43:367–378, 2000.)

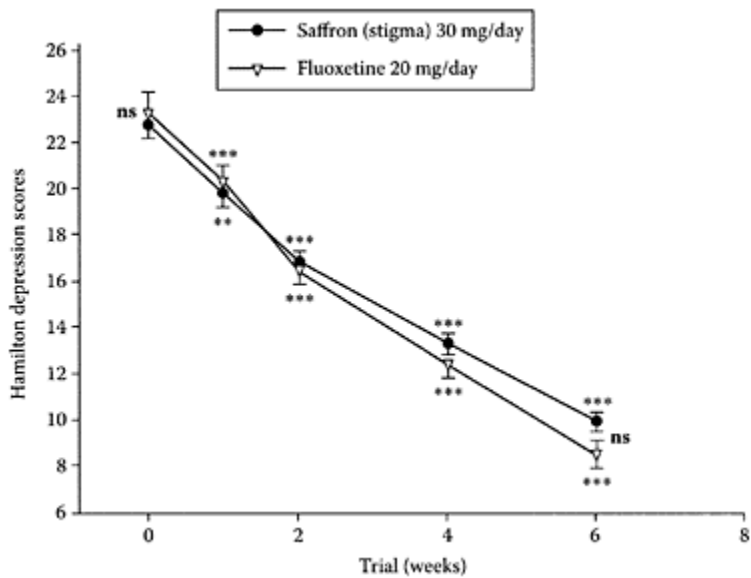


FIGURE S.88 Mean \pm S.E.M. scores of two groups of patients on the Hamilton Depression Rating Scale, (ns) Nonsignificant; (**) $p < 0.01$ and (***) $p < 0.001$. The horizontal symbols (**) and (***) were used to express statistical significance vs. their respective baseline value, and ns were used for between-group comparisons. (From Noorbala et al., *J.*

Ethnopharmacol., 97:281–284, 2005.
(With permission.)

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Sage (*Salvia officinalis*)

Sage is a common aromatic and medicinal plant native to Mediterranean countries but now grown throughout Europe and North America. The odor and aromatic taste of sage are due to its volatile oil. The plant's medicinal value resides in its crushed, dried leaves and the oil extracted from its flowers, leaves, and stems. It exhibits antibacterial qualities, inhibits viral and fungal growth (Radulescu et al., 2004), reduces perspiration and other secretions, and acts as an astringent, tightening and drying the tissues (Togel et al., 2002).

Salvia officinalis has been used in herbal medicine for many centuries. It has been suggested, on the basis of traditional medicine and its *in vitro* cholinergic-binding properties and modulation of mood and cognitive performance in humans, that *Salvia officinalis* might potentially provide a novel natural treatment for Alzheimer's disease. A

recent study demonstrated the efficacy of *Salvia officinalis* extract in the management of mild to moderate Alzheimer's disease (Akhondzadeh et al., 2003).

Caffeic acid, rosmarinic acid, and oligomers of caffeic acid, with multiple catechol groups, are all constituents of *Salvia officinalis*, with antioxidant potential with regard to their radical-scavenging activity and the stability and structure of the intermediate radicals (Bors et al., 2004). Ursolic acid is the main component in *Salvia officinalis* L. leaves that is involved in sage topical anti-inflammatory activity (Baricevic et al., 2001).

Antimutagenic properties of terpenoid fractions of sage (*Salvia officinalis*) were demonstrated by Vujosevic and Blagojevic (2004) in mammalian system *in vivo*. Sage decreases the frequency of aberrant cells, induced by a potent mutagen. The acidic polysaccharide fractions from the aerial parts of sage were found to exhibit mitogenic activities, indicating that they may have adjuvant properties (Capek and Hribalova, 2004).

Lima and coworkers (2005) recently reported that drinking a water infusion (tea) of common sage (*Salvia officinalis*) improved the liver antioxidant status, measured as GSH content, in mice and rats. Compared to water, drinking sage tea conferred some protection in the hepatocyte cultures exposed to *tert*-butyl hydroperoxide (*t*-BHP). This was particularly evident in the presence of 1 mM *t*BHP (Figure S.89). These results point to the important antioxidant contribution by sage in combating oxidative stress.

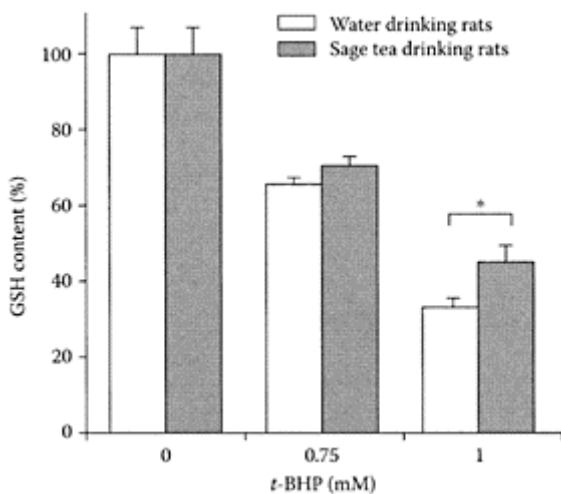


FIGURE S.89 Effect of sage-tea consumption (*in vivo* for 14 days) on *t*-BHP-induced decrease in GSH content of primary hepatocyte cultures, presented as percentage of the control. Values are mean±S.E.M., n=4. **p* <0.05, significantly different with Student's *t*-test. (From Lima et al., *J.*

Ethnopharm., 97:383–389, 2005. With permission.)

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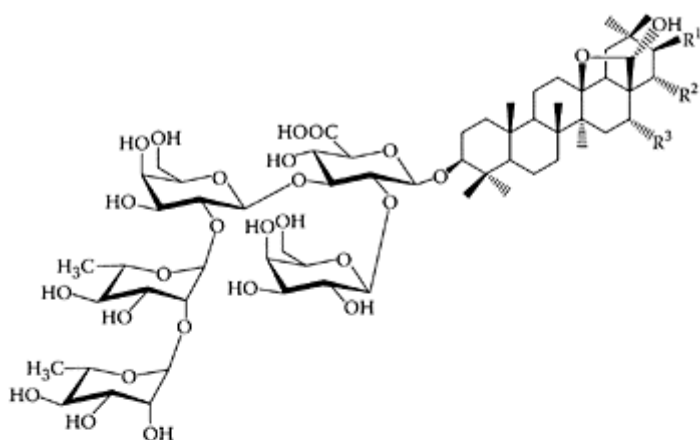
Saponins

Saponins are a group of surface-active glycosides, produced mainly by plants and some lower marine animals and bacteria (Espada and Riguera, 1997; Yoshiki et al., 1998). They consist of a sugar moiety, such as glucose, galactose, glucuronic acid, xylose, rhamnose, or methylpentose, attached to a hydrophobic aglycone (sapogenin), which can be a triterpenoid or steroid. Triterpenoid saponins are predominant in cultivated crops, while steroid saponins are found in plants used as herbs, particularly for their health-related properties (Fenwick et al., 1991). Some saponins were found by Johnson and coworkers (1986) to increase cell permeability and facilitate the uptake of substances not previously absorbed. For example, Gee and coworkers (1993) showed the ability of quinoa saponins to increase cell permeability, which could be used to enhance drug absorption by patients. In fact, Estrada et al. (1998) found that quinoa saponins could act as adjuvants for mucosally administered vaccines. Saponins from different sources were also shown to lower serum cholesterol levels in a variety of animals and humans (Al-Habori and Raman, 1998) and to have anti-inflammatory (Wei et al., 2004) and

antioxidant (Sur et al., 2001) properties. Saponin-based adjuvants stimulated the immune system, as well as enhanced antibody production at low-dose levels (Oda et al., 2000). The adjuvant activity was attributed to branched sugar chains (Bomford et al., 1992) or aldehyde groups (Kensil, 1996). Saponins from different sources were found to inhibit cancer cells *in vitro* (Podolak et al., 1998). Triterpenoid saponins from *Acacia vitoriae* were reported to selectively inhibit the growth of tumor in human breast-cancer cell lines by arresting cell cycle or by apoptosis in leukemia-cell lines (Mujoo et al., 2001). Triterpene saponins also showed a prominent IL-2-inducing activity, which may explain the mechanism involved in their immunomodulatory and anticancer effects (Yesilada et al., 2005). Francis and coworkers (2002) reviewed the biological action of saponins in animal systems. Recently, triterpenoid saponins isolated from the leaves of the Vietnamese medicinal plant *Maesa balansae*, showed *in vitro* and *in vivo* activity against the tropical protozoal parasite *Leishmania infantum* (Scheme S.54) (Germonprez et al., 2005).

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Saponin	R ¹	R ²	R ³
1			OH
2			OH
3			OH
4			OH
5			OAc
6			UAc

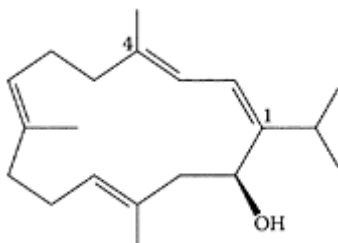
SCHEME S.54 Six triterpenoid saponins extracted from *Maesa balansae*. (From Leonard et al., *J. Chromatogr. A*, 1012:39–46, 2003. With permission.)

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Sarcophytol

A Sarcophytol A (SaA) is a cembrane-type diterpene isolated from the marine soft coral *Sarcophyton glaucum*. It showed anti-cancer and cancer-preventive effects in two animal models: transplanted human pancreatic-cancer cells in nude mice and pancreatic

carcinogenesis induced by N-nitrobis-(2-hydroxypropyl) amine in Syrian golden hamsters (Yokomatsu et al., 1994).



Sarcophytol A. (From Li et al., *Tetrahedron Lett.*, 40:965–968, 1999. With permission.)

SaA also provided significant protection against the induction of genetic damage in human lung cells exposed to tobacco-specific nitrosamines (Weitberg and Corvese, 1999).

Recently, the natural cembranolide sarcophine and its lactone ring-opened analogue were oxidized to prepare hydroxylated derivatives, which were shown to have higher activity than the chemopreventive agent Sarcophytol A (Katsuyama et al., 2002).

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Saskatoon berry

The Saskatoon (*Amelanchier alnifolia*) is a small to large shrub, or a small



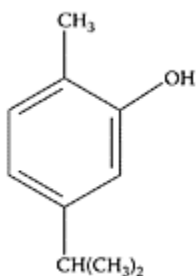
tree, which belongs to the rose family. The Saskatoon, an important food source, was also used as a source wood and a medicinal plant. Today, Saskatoons are used in a wide variety of ways, from pies, jams, jellies, syrups, ice cream toppings, wine, liqueurs, and flavor concentrates to components of baked goods. The methanolic extract of *Amelanchier alnifolia* was found active against an enteric coronavirus, demonstrating antiviral activities at the noncytotoxic concentrations (McCutcheon et al., 1995)

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Savory (*Satureja hortensis* L.)

Savory, an annual herb of the Lamiaceae family, is used as a condiment, as well as in folk medicine, for treating infectious diseases. It contains an essential oil composed of thymol, although the main component is carvacrol, a positional isomer of thymol (30 percent to 45 percent), as well as *p*-cymene (max. 30 percent), γ -terpinene, α -pinene (8 percent), dipentene, borneol, 1-linalool, terpineol, and 1-carvone. Antimicrobial and antioxidant tests by Gulluce



Carvacrol. (From De Vicenzi et al., *Fitoterapia*, 75:801–804, 2004. With permission.)

et al. (2003) showed the essential oil exhibited antimicrobial activities against all 23 bacteria and 15 fungi and yeast species tested, while linoleic-acid oxidation was inhibited by 95 percent. The evaluation of antioxidant power of glycosidically bound volatile aglycones from savory showed the antioxidative activity possessed by these compounds was comparable to that of the essential oil (Radonic and Milos, 2003). The antioxidant properties of a crude extract and its purified ethyl acetate-soluble fraction from the aerial material of savory was recently demonstrated by Dorman and Hiltunen (2004) using an Fe(III) reductive and DPPH, ABTS⁺, and hydroxyl free-radical-scavenging assays. Chorianopoulos et al. (2004) reported that essential oils extracted from the *Satureja* species represented an inexpensive source of natural antibacterial compounds for potential use in food systems to prevent the growth of foodborne bacteria and extend the shelf life of the processed food. The antibacterial activity of a number of essential oils, including savory oil, was found to be effective against vaginal microorganisms responsible for infectious gynecological diseases (Arnal-Schnebelen et al., 2004). Other species of savory plants were reported to have antinociceptive (Hajhashemi et al., 2002) and anti-inflammatory (Uslu et al., 2003) effects.

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Saw palmetto

see also Palmetto berries Saw palmetto (*Serenoa repens*) is a North American native plant whose berries are used for medicinal purposes. A letter to the editor by Champault and coworkers in 1984 first highlighted the pharmacological benefits of saw palmetto for the treatment of benign prostatic hyperplasia. It has since become the treatment for enlarged prostate or benign prostatic hyperplasia (BPH) in Europe (Wilt et al., 1998). Using a six-month, randomized trial, Veltri et al. (2002) found that treating men with symptomatic BPH with a saw palmetto herbal blend altered DNA chromatin structure and organization in prostate epithelial cells, suggesting a possible molecular basis for its therapeutic effect. Recent studies in the United States by Gerber et al. (2000) and Gong and Gerber (2004) showed that saw palmetto improved urinary function for those suffering from BPH.

The efficacy of saw palmetto appears to be similar to medications, such as finasteride, but it is better tolerated and less expensive. There are no known drug interactions with saw palmetto, and reported side effects are minor and rare. It was also used to treat chronic prostatitis, but currently there is no evidence of its efficacy (Gordon and Shaughnessy, 2003).

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Sea buckthorn (*Hippophae rhamnoides* L.)

Sea buckthorn, a temperate, hardy bush growing in Central Asia and Europe, produces nutritious and delicious berries (Roussi, 1971). The oil from the berries of sea buckthorn has been used in Chinese medicine for many centuries for treating cardiovascular disease.

In fact, sea-buckthorn berries, particularly the alcohol extract of the twigs, was reported to inhibit thrombus

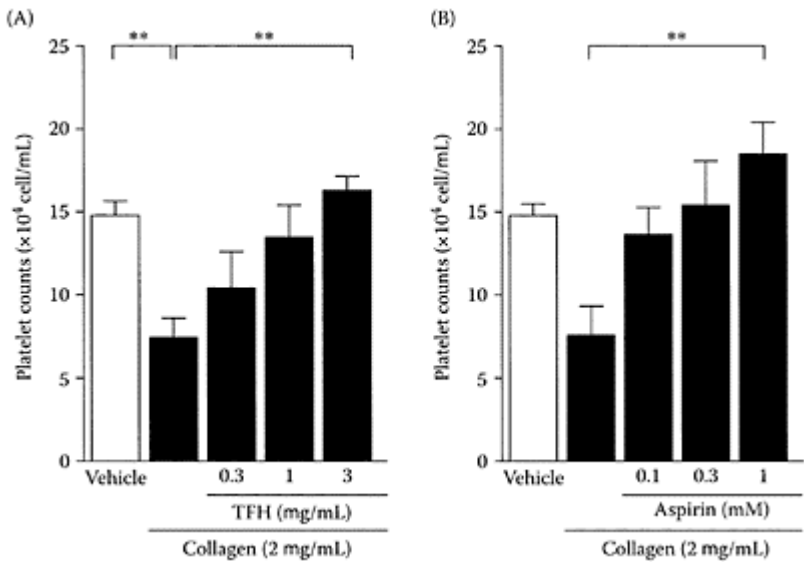


FIGURE S.90 Effects of (A) TFH and (B) aspirin on platelet aggregation induced by collagen (2 μ g/mL) in whole blood from five mice. An open column indicates platelet counts in the tubes with added vehicle without collagen. Data are presented as means \pm S.E.M. **, $p<0.01$ by Bonferroni's multiple comparison test. (From Cheng et al., *Life Sci.*, 72:2263–2271, 2003. With permission.)

formation or platelet aggregation (Xu and Chen, 1991). Sea buckthorn is rich in antioxidants, tocopherols (Luhua et al., 2004), carotenoids, and vitamin C, as well as phytosterols, such as sitosterol (Field et al., 1997). In the sea-buck-thorn pomace extract, the oligomeric proanthocyanidins accounted for 75 percent of the total antioxidant activity (Rosch et al., 2004). Using a supercritical extract of sea-buckthorn oil, Johansson and coworkers (2000) showed it inhibited platelet aggregation. Cheng and coworkers (2003) reported that a total flavone (TFH) extract from sea buckthorn exhibited a similar inhibitory effect to aspirin on platelet aggregation induced by collagen in mouse femoral artery (Figure S.90). This ability to prevent *in vivo* thrombogenesis, similar to aspirin, suggested sea buckthorn may help prevent cardiac and cerebral thrombosis.

Eccleston et al. (2002) showed sea-buck-thorn juice was rich in antioxidants and moderately decreased the susceptibility of LDL to oxidation. An earlier study by Yang and coworkers (1999) found α -linolenic acid in sea buckthorn had a beneficial effect on atopic dermatitis (AD), a condition in which the skin is dry, scaly, and itchy with eczematous inflammation and lesions. Sea buckthorn was also reported to be a hopeful drug for prevention and treatment of liver fibrosis (Gao et al., 2003).

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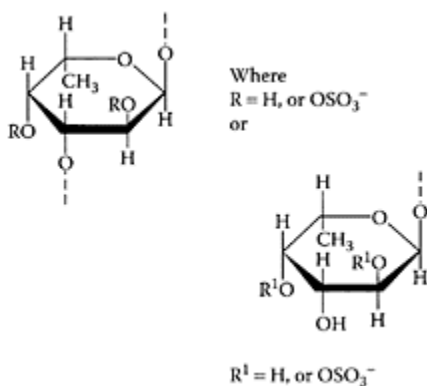
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Sea cucumbers

Sea cucumbers or *Holothuroidea*, are an abundant and diverse group of worm-like, soft-bodied echinoderms. They are ubiquitous in the marine environment but particularly diverse in tropical, shallow-water coral reefs. In the Southeast Asia regions, sea cucumbers are used as food supplements and as traditional remedy for wounds (Perchenik, 1996), parasitic skin infections (Shimada, 1969), and other ailments, such as backache, joint pain, and stomach and mouth ulcers.

Sea cucumber contains a wide range of nutrients, including collagen, marine protein, essential fatty acids, and antioxidants, including vitamin E and minerals (Hawa et al., 1999).

A few species of sea cucumbers showed antibacterial activity (Ridzwan et al., 1995), and glycosphingolipids from the sea cucumber had neuritogenic activity toward the saponin biosynthesis (Kerr and Chen, 1995). Yamada (2002) isolated pheochromocytoma cell line C-type mannan-binding lectins from various species of sea cucumbers exhibiting relatively high agglutinating activity (Bulgakov et al., 2000). Recently, Kariya et al. (2004) isolated two types of fucan sulfates, types A and B, from sea cucumber (*Stichopus japonicus*) that were potent inhibitors of osteoclastogenesis. Type A consisted of a backbone of (163)-linked fucosyl



SCHEME S.55 Hypothetical structures of type A and type B fucan sulfates. Both have a backbone of (1→3)-linked fucose residues substituted with fucosyl residues at C-2 and C-4. Sulfate substitution(s) occur at C-2 and C-4 position(s). (Kariya et al., *Carbohydr. Res.*, 339:1339–1346, 2004. With permission.)

residues substituted at C-4 with the fucosyl residues sulfated at C-2/C-4 (Scheme S.55).

Type B consisted of unbranched (163)-linked fucosyl residues with sulfate substitution(s) at C-2 and/or C-4. The presence of either type A or B inhibited osteoclastogenesis in an *in vitro* osteoclast assay by 99.8 percent and 96.3 percent, respectively, compared to the control (Figure S.91). The potent inhibition of osteoclastogenesis by fucan sulfates points to their potential for treating some of the symptoms associated with osteoporosis and rheumatoid arthritis.

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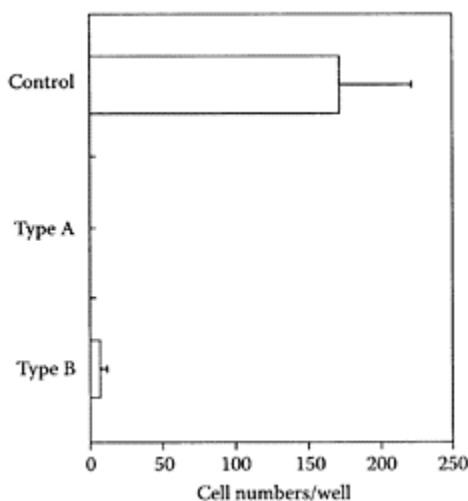


FIGURE S.91 Inhibitory effects of types A and B fucan sulfate on an *in vitro* osteoclast-formation assay system. Data expressed as mean \pm SD (n=3) taking the control as 0 percent. (From Kariya et al., *Carbohydr. Res.*, 339:1339–1346, 2004. With permission.)

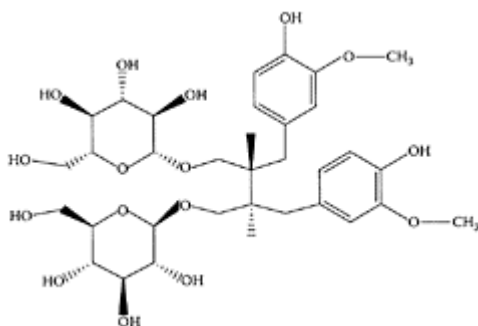
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Secoisolariciresinol diglycoside

see also Lignans Secoisolariciresinol diglycoside (SDG) is a plant lignan most notably found in flaxseed (linseed). SDG is classified as a phytoestrogen with a weak estrogenic activity. The level of SDG in flaxseed typically varies between 0.6 percent and 1.8 percent. Following ingestion, SDG is converted to the aglycone Secoisolariciresinol, which is then metabolized to the mammalian lignans enterolactone and enterodiol. Most of the effects of oral SDG are mediated by enterolactone and enterodiol.



Secoisolariciresinol diglucoside. (From Coran et al., *J. Chromatogr. A*, 1045:217–222, 2004. With permission.)

SDG, enterolactone, and enterodiol exhibited a number of antioxidant activities (Kitts et al., 1999), including inhibition of lipid peroxidation and scavenging of hydroxy radicals. SDG inhibited mammary-tumor development (Rickard et al., 2000), as well as delayed the progression of dimethylbenz[*a*]anthracene-induced mammary tumorigenesis (Rickard et al., 1999). Supplementation with SDG reduced pulmonary metastasis of mice melanoma cells and inhibited the growth of metastatic tumors formed in the lungs (Li et al., 1999). This was evident by a significant decrease in the mean tumor cross-sectional area and volume in a dose-dependent manner compared to the control (Table S.61).

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TABLE S.61
Effect of Dietary Supplementation with SDG on Pulmonary Metastasis of Melanoma Cells in Mice

Group	Mice <i>n</i>	Mice with Lung Tumors		Tumors/mouse		Range
		1–50 Tumors	>50 Tumors ^a	Median ^b	Mean±SE	
Control	27	11	16	62	64±8	10–180
SDG						
71 µmol/kg	27	19	8	38	43±5	8–117
147 µmol/kg	28	22	6 ^a	36	42±4	9–96
293 µmol/kg	27	21	6 ^a	29 ^b	33±4	4–86

^a Significantly different from the control, *p* <0.05. Data were analyzed using Fisher’s exact test.
^b Significantly different from the control, *p* <0.01. Data were analyzed using the Kruskal-Wallis nonparametric and Dunn’s multiple comparison test.

Source: From Li et al., *Cancer Lett.*, 142:91–96, 1999. With permission.

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Selenium

Selenium, a trace element essential in small amounts, can be toxic when taken in larger amounts. The levels in the body depend mainly on the amount of selenium in the diet, which is a function of the selenium content of the soil. Selenium is required for the functioning of more than 30 known selenoproteins, essential for normal functioning of the immune system (He et al., 2004), thyroid gland (Zagrodzki et al., 2001), and normal development, growth, metabolism, and defense of the body (Dodig and Cepelak, 2004; Kohrl et al., 2000).

A large number of studies confirmed that selenium supplementation plays a preventive and therapeutical role in diseases, such as male infertility (Foresta et al., 2002), viral infections (Broome et al., 2004), HIV (Kupka et al., 2004), cancer (recently reviewed by Patrick, 2004), and cardiovascular (Alissa et al., 2003) and autoimmune diseases (Gartner and Gasnier, 2003).

Selenium is an essential constituent of a number of enzymes, some of which have anti-oxidant functions. A deficiency of this element in animals renders them susceptible to injury by certain types of oxidative stress (Burk, 2002). In addition, selenomethionine catalyzes the reduction of peroxynitrite and low-molecular-weight organoselenium, compounds of pharmacologic interest known to catalyze the reduction of hydroperoxides or peroxynitrite with various cellular-reducing equivalents (Klotz et al., 2003). Oxidative stress plays an important role in vascular degenerative lesions observed in diabetes. Selenium is the cofactor of glutathione peroxidase, which is associated with thrombosis and cardiovascular complications of diabetes (Faure, 2003).

Analyses of pooled data from 1763 trial participants showed that statistically, individuals whose blood-selenium values were in the highest quartile (median =150 ng/mL) had significantly lower odds of developing new adenomas compared with those in the lowest. The inverse association between higher blood-selenium concentration and adenoma risk supports previous findings indicating that higher selenium status may be related to decreased risk of colorectal cancer (Jacobs et al., 2004).

Popova (2002) investigated the influence of neonatal selenium exposure on spontaneous liver-tumor formation in adult mice. Selenium was administered to pregnant CBA mice during their last week of pregnancy and for 10 days following parturition. There was a significant reduction in the incidence of spontaneous hepatomas in the adult male progeny, but not in adult females. This indicated that neonatal selenium altered hepatoma incidence in a sex-dependent manner.

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Senega (*Polygala senega*)

This perennial herb grows in central and western North America. The name of the genus, *Polygala*, means “much milk,” alluding to its own profuse secretions and their effects. “Senega” is derived from the Seneca tribe of North American Indians, among



whom the roots were used as a remedy for snake bites. The root contains polygalic acid, virgineic acid, pectic and tannic acids, yellow, bitter, coloring matter, cerin-fixed oil, resin, traces of volatile oil (a mixture of valeric ether and methyl salicylate), 7 percent sugar, from 2 percent to 5 percent senegin (Saitoh et al., 1994), malatesgum, woody fiber, salts, aluminum, silica, magnesium, and iron (Moes, 1966). Fresh senega root has a pleasant odor due to its content of approximately 0.1 percent methyl salicylate. The active ingredient, however, is a complex mixture in the root of triterpenoid saponins in a concentration ranging from 8 percent to 16 percent (Yoshikawa et al., 1996). The

saponins act by local irritation on the lining of the stomach, causing nausea that in turn stimulates both bronchial secretion and the sweat glands.

During the early 19th century, senega root was used as an expectorant cough remedy. Today, senega root is used to treat bronchitis, tracheitis, emphysema, and inflammation of the respiratory tract (Kuribara and Tadokoro, 1989). The saponins suppress coughing, while their detergent activity breaks up phlegm (Kantee, 1973). Senega is also believed to stimulate bronchial mucous-gland secretion. Saponins in senega root may hold some potential for treatment of noninsulin-dependent diabetes (Kako et al., 1996). Senegose A, senegin II, senegin III, and senegasaponin b, hair-regrowth substances, were isolated from *Polygala senega* by Ishida et al. (1999).

Recently, senega saponins were reported to display immunopotential activity to protein and viral antigens, suggesting their potential role as vaccine adjuvants to increase specific immune responses (Estrada et al., 2000)

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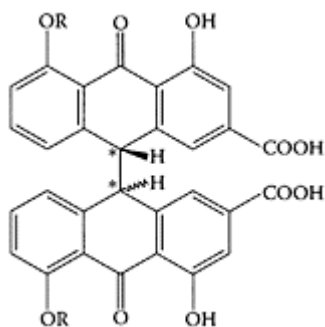
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Senna

Senna, a traditional Chinese medicine, possesses multiple pharmacological activities. In particular, it can promote the motility and secretion of the gastrointestinal tract (Krumbiegel and Schulz, 1993; Valverde et al., 1999). However, its application is greatly

restricted by its toxicity (Stickel et al., 2001, Adam et al., 2001). The body-weight gain (males only) of animals receiving 750 or 1500 mg/kg per day was reduced significantly and, due to the laxative properties of senna, water consumption increased, and notable changes in electrolytes in both serum and urine were observed (Mengs et al., 2004). Senna plants are small shrubs of *Leguminosae*, cultivated in Somalia, the Arabian peninsula, and near the Nile River. Tinnevely senna is obtained from cultivated plants, mainly in South India and Pakistan. The senna pods (fruits) are collected during the same

SCHEME S.56 Chemical structures of sennidins and sennosides. (From Hazra et al., *J. Chromatogr. B*, 812:259–275, 2004. With permission.)

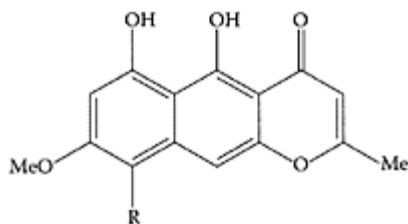


Compound	R
Sennidin A (10,10'-trans)	H
Sennidin B (10,10'-meso)	H
Sennoside A (10,10'-trans)	Glu
Sennoside B (10,10'-meso)	Glu

period as the leaves, then dried and separated into various qualities. The active principle of senna was first isolated and characterized by Stoll in 1941. The isolated glycosides were identified and attributed to the anthraquinone family (Scheme S.56). They were named sennosides A, B, C, and D. The active constituents in the pods and in the leaves are similar, but are present in larger quantities in the pods (Franz, 1993).

Much attention is being paid to senna effects on the regulation of gastrointestinal motility (Tian et al., 2000; Zhang et al., 2000). Wang et al. (2002) showed senna caused diarrhea and enhanced gastrointestinal motility through digestive-tract administration. Long-term gastric administration of senna induced inflammatory changes and cell damage in the whole gastrointestinal tract. The researchers suggested that the differential proteins screened from the colonic tissues of the model mice might mediate the enhancing effect of senna on gastrointestinal motility.

Quinquequangulin and rubrofusarin are two known antimycobacterial natural products



Quinquangulin (R=CH₃) and ribrofusarin (R=H). (From Barbosa et al., *Biochem. System. Ecol.*, 32:363–365, 2004. With permission.)

extracted from the stem and fruits of senna (Graham et al., 2004.). The piperidine alkaloid cassine is another antimicrobial compound isolated from the leaves of *Senna racemosa* (Sansores-Peraza et al., 2000).

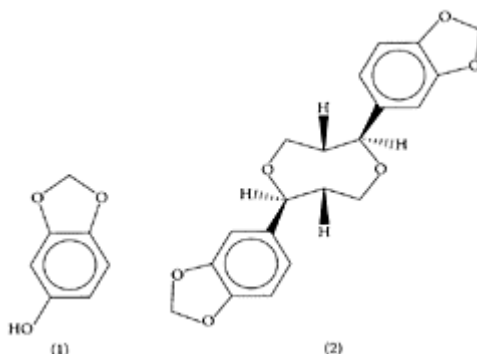
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Sesame

Sesame (*Sesamum indicum* L.), an important oilseed crop in India, Sudan, China, and Burma, has been used as a healing oil for thousands of years. Sesame seeds have a higher oil and lower protein content than soybean, with the oil content ranging from 46.4–52.0 percent, and the protein content ranging from 19.8–24.2 percent. The fatty-acid composition of sesame seeds is oleic (40.4–44.9 percent), linoleic (37.7–43.4 percent), palmitic (9.1–9.8 percent), and stearic (4.8–6.1 percent).

The mechanism by which a diet containing 24 percent sesame oil reduces levels of serum and liver cholesterol, liver LDL cholesterol, and liver lipids is not known. However, the high degree of unsaturation (85 percent) of sesame oil and the presence of linoleic acid may be important factors (Satchithanandam et al., 1996). Linoleic acid is also known to have anti-neoplastic properties. When Salerno and Smith (1991) tested lipase-digested sesame oil and undigested sesame oil, they found that both inhibited the growth of three malignant colon-cell lines. Thus, sesame contains *in vitro* antineoplastic properties. Lignans and lignan glycosides, such as sesamol dimer, sesamin, sesamol, sesaminol triglucoside, and sesaminol diglucoside, isolated from sesame-methanolic extract, showed a high capacity for free-radical scavenging with the DPPH system (Suja et al., 2004). These lignans, in combination with α -tocopherol, showed a lag period in the time course of cumene hydroperoxide-mediated lipid peroxidation and a decreased rate of thiobarbituric acid reactive-product formation, suggesting recycling of α -tocopherol. Further work by Suja and coworkers (2005) showed the antioxidant activity of a crude methanol extract obtained from sesame cake was comparable to BHT at 200 ppm. In contrast, the corresponding



Sesamol (1) and sesamin (2). (From Chavali and Forse, *Prostaglandins Leukot. Essent. Fatty Acids*, 61:347–352, 1999. With permission.)

purified extract exhibited far superior antioxidant properties to BHT at 5, 10, 50, 100, and 200 ppm levels. A typical result is shown in Figure S.92 using the thiocyanate method linoleic-acid emulsion system. Prasad et al. (2005) reported that the antioxidant

properties of sesamol provided potent phytoprotection to lymphocytes against UVB radiation.

An increase in reported sesame-induced allergic reactions led Wolff et al. (2004) to identify and characterize the linear B-cell epitopes, the major allergen of sesame seed, which might provide a better understanding of the functional role the allergens play and might have implications for immunodiagnosis and probably immunotherapy. A single dose of sesame oil reduced lipid peroxidation 6 h after endotoxin intoxication. Furthermore, sesame oil given 6 h after

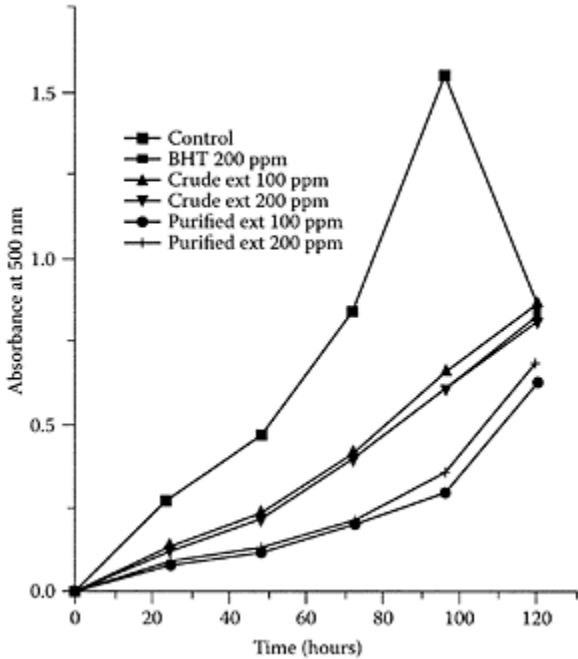


FIGURE S.92 Antioxidant activity of sesame extracts and BHT by the thiocyanate-cyanate method linoleic acid system. (From Suja et al, *Food Chem.*, 91:213–219, 2005. With permission.)

cecal ligation and puncture significantly increased survival rate. These data suggest that sesame oil could be used as a potent antioxidant to reduce oxidative stress after the onset of sepsis in rats (Hsu and Liu, 2004).

Chen et al. (2005) recently suggested that the overall vascular fibrinolytic capacity may be enhanced by using sesamol, which regulates plasminogen activator gene expression. Sesamol is also known to reduce the synthesis of the coenzyme NADPH, which led Jacklin et al. (2003) to study the effect of oxidants on tumor and vascular

endothelial cells. In preliminary studies on the effect of sesamol alone, it was clear that the compound demonstrated marked cytotoxicity.

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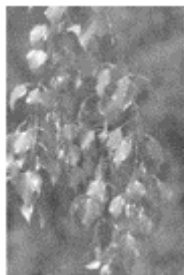
Sho-saiko-to

Sho-saiko-to (SST), introduced into Japan as an oriental classical medicine from China approximately 1,500 years ago, is currently the most representative Kampo medicine (traditional Japanese medicine). SST is used to treat chronic hepatitis and cirrhosis. Many experimental and clinical studies have demonstrated the various pharmacological effects of SST (Kusunose et al., 2002; Tajiri et al., 1991; Geerts and Rogiers, 1999). SST is a mixture drug of medicinal herbs prepared from the hot-water extraction of seven raw materials. Fifteen major, low-molecular compounds (i.e., baicalin, wogonin-7-O-

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Silver birch (*Betula pendula*)

Betula, of the family Betulaceae, commonly known as silver



birch, grows mainly in the northern hemisphere from Eastern Europe to the northern parts of China and Japan. Different parts of *Betula* species have various medicinal applications, which in part is due to their essential oils. More than 50 compounds were identified in the essential oil from *Betula* species. The main components were α -copaene (12 percent and 10 percent), germacrene D (11 percent and 18 percent), and δ -cadinene (11 percent and

15 percent) (Betül et al., 2004). Some of the caryophyllene derivatives were evaluated for antimicrobial activity (Demirci et al., 2000a, b).

The medicinal parts are the bark, leaves, buds, sap, or juice or their processed products, which are used to treat diseases, such as urinarytract disorders, skin diseases, severe infections, and inflammations. Furthermore, *B. pendula* flavors are used commercially as aroma and flavoring for alcoholic beverages. Other uses include applications in cosmetics.

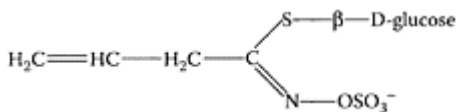
Diverse phytochemical investigations of *Betula* species have shown they contain mainly phenolics, flavonoids, tannins, saponins, glycosides, sterols, and terpene derivatives (Demirci et al., 2000).

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Sinigrin

Sinigrin, 2-propenyl glucosinolate, is a common glucosinolate in *Brassica* vegetables known to possess anticarcinogenic activity. Elfoul et al. (2001) showed that sinigrin can be



Sinigrin. (From Jen et al., *J. Chromatogr. A*, 912:363–368, 2001. With permission.)

hydrolyzed by a *Bacteroides thetaiotaomicron* strain of human origin to yield allyl isothiocyanate (AITC) in the large bowel of rats inoculated with this bacterium. Three other strains of Bifidobacterium sp., *B. pseudocatenulatum*, *B. adolescentis*, and *B. longum*, from human intestinal tract were also able to digest sinigrin (Cheng et al., 2004). This local release of isothiocyanates may explain the protective effect of cruciferous vegetables on the colon epithelium.

Depending on target tissue and the type of compound, different mechanisms of action have been suggested to explain the anticarcinogenic actions of glucosinolates and their breakdown products, among which are the isothiocyanates (ITCs). The most frequently proposed cancerpreventive mechanisms are modulation of the activities of phase I (cytochrome P450s) and phase II (glutathione-S-transferase, UDP-glucuronosyl-transferase, and quinone reductase) biotransformation enzymes (Vang et al., 1999), redox regulation antiproliferation, and induction of cell-cycle arrest and by increasing the rate of apoptosis in cancer cells (Yu et al., 1998; Yang et al., 2002).

The production of allyl isothiocyanate from sinigrin was investigated in a dynamic, *in vitro* large-intestinal model, after inoculation with a complex microflora of human origin. Peak levels of allyl isothiocyanate were observed between 9 and 12 h after the addition of sinigrin. The conversion rate was remarkably higher if different individual human microflora were used. Between 10 percent and 30 percent (mean 19 percent) of the sinigrin was converted into allyl isothiocyanate (Krul et al., 2002)

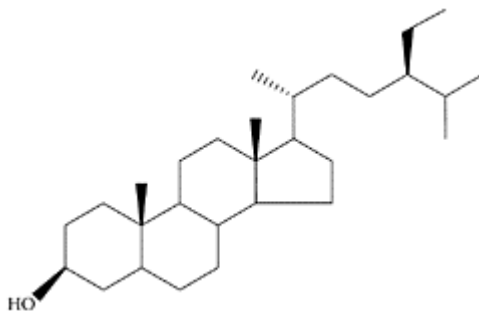
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Sitostanol

see also Phytosterols Sitostanol, the saturated derivative of plant sterol β -sitosterol, is a natural dietary component with serum cholesterol-lowering properties (Perez-Jimenez et

al., 1995; Terry et al., 1995; Jones et al., 1999). However, it is not found in significant amounts in plants but comprises up to 20 percent of the phytosterols extracted from tall oil (Ling and Joseph, 1995). The lowering of serum cholesterol by plant sterols is believed to be the



Sitostanol. (Adapted from Moreau et al., *Prog. Lipid Res.*, 41:457–500, 2002.)

result of an inhibition of cholesterol absorption in the small bowel (Normen et al., 2000), although increased bile-acid excretion has also been suggested (Becker et al., 1993). Recently, it has been reported that unesterified sitostanol is more effective in inhibiting cholesterol absorption and reducing LDL cholesterol than acetate or oleate esters (Sudhop et al., 2003).

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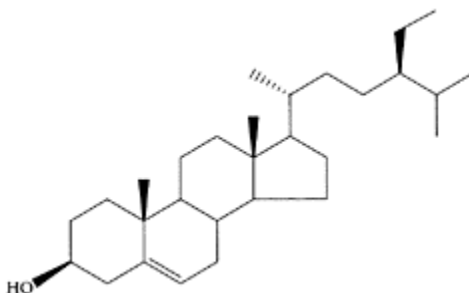
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Sitosterol

see also Phytosterols and Sitostanol Sitosterol, or β -sitosterol, belongs to dietary phytosterols. The various biological activities of phytosterols, anti-inflammatory, cholesterol-lowering, antimicrobial, antibacterial, and antifungal effects, are reviewed by Tapiero et al. (2003), Ostlund (2004), and Qullez et al. (2003). Recently, the antitumor and chemopreventive activity of sitosterols were studied by Valchakova et al. (2004). They demonstrated that sitosterol inhibited colon and breast-cancer development at various stages of tumor development, including inhibition of tumorigenesis, inhibition of tumor promotion, and induction of cell differentiation. It also effectively inhibited invasion of tumor cells and



β -Sitosterol. (Adapted from Moreau et al., *Prog. Lipid Res.*, 41:457–500, 2002.)

metastasis. Ju et al. (2004) also reported that dietary β -sitosterol protected against E(2)-stimulated MCF-7 tumor growth and lowered circulating E(2) levels.

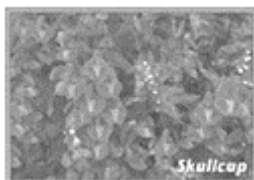
Circulating levels of β -sitosterol can be affected by dietary modification. Thus, β -sitosterol can be used as a biomarker of exposure in observational studies or as a compliance indicator in dietary-intervention studies of cancer prevention (Muti et al., 2003).

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Skullcap (*Scutellaria lateriflora* L.)



Skullcap is a perennial member of the mint family, with 300 *Scutellaria* species growing worldwide. It has been traditionally used as a sedative and to treat various nervous disorders, such as anxiety (Awad et al., 2003). Chinese skullcap is also used in Traditional Chinese Medicine to treat tumors. Early laboratory studies investigating this traditional use showed possible preventive involvement in bladder, liver, and other types of cancers (Udintsev et al., 1990). The main constituents found in the plant are scutellarin, a flavonoid glycoside, together with many other flavones, catalpol, other volatile oils, bitter iridoids, and tannins (Popova et al., 1972, Popova, 1974).

In vivo animal-behavior trials, performed to test anxiolytic effects in rats orally administered skullcap extracts, demonstrated that the flavonoid baicalin, its aglycone baicalein, and the amino acids GABA and glutamine may play a role in anxiolytic activity. This is not unexpected, as baicalin and baicalein are known to bind to the benzodiazepine site of the GABA receptor and GABA is the main inhibitory neurotransmitter (Awad et al., 2003).

Recently, Baikal-skullcap extract was reported to potentiate the anti-metastatic effect of cyclophosphamide in mice with Lewis lung carcinoma. It modulated cytotoxic activity of natural-killer cells and peritoneal macrophages during tumor growth (Kaplya et al., 2004).

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Sorghum (*sorghum vulgare*)

Sorghum is the major food crop in the semiarid regions of Africa and Asia. It provides a component to the diets of many people in the form of unleavened



bread, boiled porridge or gruel, malted beverages, and specialty foods, such as popped grain and beer (Anglani, 1998). A syrup is produced from sweet sorghum. The crop is also used for building material, fencing, fodder for animals, and for brooms. In the United States, sorghum grain is used primarily for livestock feed, and the stems and foliage for green chop, hay, silage, and pasture.

A comparison of the nutritional and chemical parameters of 10 varieties of sorghum showed components to range from lipids (2.70–3.75 percent), raw fiber (60.0–64.7 percent), protein (9.01–11.43 percent), no nitrogen extract (77.65–83.07 percent), starch (60.5–64.20 percent), tannin (2.50–10.16 mg/g), and total calories (380–4000 kcal). Ash content, with values of 1.17–1.91 percent, protein digestibility (23.8–38.8 percent), and *in situ* starch (54.4–66.6 percent) were not statistically different (Torres Cepeda et al., 1996)

Sorghum is a rich source of various phytochemicals, including tannins, phenolic acids, anthocyanins, phytosterols, and policosanols (Awika and Rooney, 2004). These phytochemicals are known to impact human health. Sorghum fractions possess high

antioxidant activity *in vitro*, relative to other cereals or fruits. Epidemiological studies suggest that, in comparison to other cereals, sorghum consumption reduces the risk of certain types of cancer in humans. Kamath et al. (2004), using the DPPH model system for assessing antiradical properties, recently identified various extracts from sorghum flour that exhibited significant, greater antioxidant activity than BHT (Figure S.93).

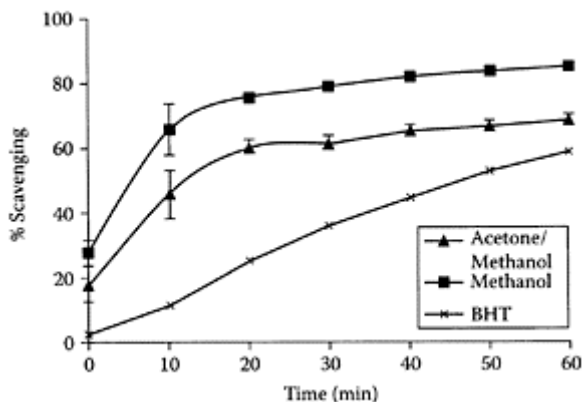


FIGURE S.93 Effect of subfractions of methanol extracts on quenching DPPH radicals-time related effect. 50 μ L (0.2 mg) of either extract of sorghum was employed for quenching. An equal volume of respective solvents was used in control. 50 μ L (10 mM) BHT was used. Each value represents mean \pm standard error (n=6). (From Kamath et al., *J. Cereal Sci.*, 40:283–288, 2004. With permission.)

Even though they were unable to correlate anti-oxidant activity and phenolic content, diets rich in sorghum could still be helpful in combating chronic diseases involving free radicals. This explains why sorghum phytochemicals promote cardiovascular health and are involved in cancer prevention (Awika and Rooney, 2004).

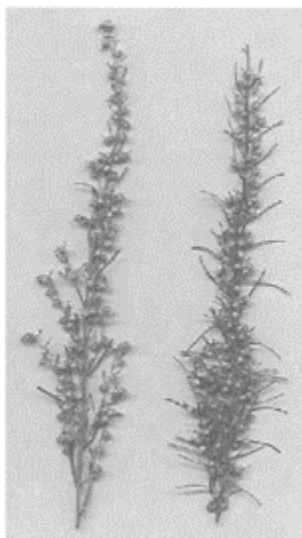
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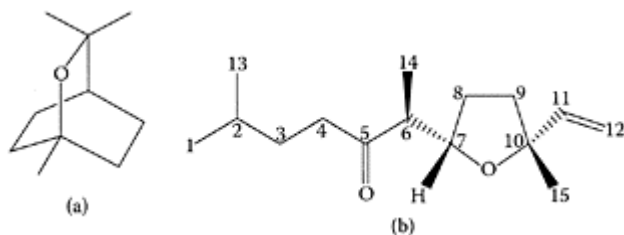
Southernwood (*Artemisia abrotanum*)

There are two different cultivated strains of southernwood. The traditional type has a vague, lemon-like smell, while the more recently bred type has an even more intense and dominant smell. Despite their significant bitterness, the leaves of both types are well-suited for culinary usage. Various sources reported different compositions for the essential oil (0.2 percent), with some claiming absinthol as the main component, while others report the heterocyclic sesquiterpenes davanol and davanone plus carlinene and 1,8-cineol. Among the nonvolatile constituents reported are the alkaloid abrotin and coumarins. Although southernwood contains significant amounts of bitter sesquiterpene lactones (absinthin) and the glycoside rutin, it is still less bitter than its close relative, wormwood.



A nasal-spray formulation containing an extract of *Artemisia abrotanum* L. was developed for therapeutic use in patients with allergic rhinitis and other upper-airway disorders. The extract used contains a mixture of essential oils (4 mg/mL) and flavonols (2.5 microg/mL), of which some components have been shown to possess anti-inflammatory, expectorant, and spasmolytic, as well as antiseptic and antimicrobial, activities. The most important constituents in the essential-oil fraction are 1,8-cineole,

linalool, and davanone, while the flavonol fraction contains centauredin, casticin, and quercetin dimethyl-ethers (Remberg, 2004).



Structures of 1,8-cineole (a) and davanone (b) (Adapted from Tisevec et al., *Biochem. Systems Ecol.*, 32:525–527, 2004; Silvester et al. *Ind. Crops Prod.*, 12:53–56, 2000)

Lactones and sesquiterpenes, isolated from the methanol extract of the aerial parts of *Artemisia sylvatica*, displayed inhibitory activity on the LPS-induced NF- κ B activation, NO production, and TNF- α production (Jin et al., 2004). *Artemisia iwayomogi* extract also inhibited mast-cell-derived, immediate-type allergic reactions and involvement of intracellular Ca(2+), proinflammatory cytokines, p38 MAPK, and NF- κ B (Kim et al., 2005). These results support the pharmacological use of *Artemisia sylvatica* and *Artemisia iwayomogi*, which have been employed as herbal medicines for inflammation treatment.

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Soybeans

see also Daidzein and Genistein A large number of components contribute to the diverse biological activities of soybeans: hormonal, immunological, bacteriological, and digestive effects. These components include isoflavones (genistein, daidzein, biochanin), saponins, Kunitz inhibitor, Bowman-Birk inhibitor, soyacystatin, phytoestrogens, Maillard products, soybean hydrophobic protein, soy allergens, lecithins, allergens, raffinose, stachyose, and 2-pentyl pyridine (Csaky and Fekete, 2004).

Soy isoflavones (genistein, daidzein, biochanin) are known to protect against different cancers (Sarkar and Li, 2003), cardiovascular disease (Hasler, 2002), and bone loss (Harkness, 2004). Many studies have demonstrated the effect of soy isoflavones on specific target molecules and signaling pathways, cell proliferation and differentiation, cell-cycle regulation, apoptosis, angiogenesis, cell adhesion and migration, metastasis, and activity of different enzymes. Isoflavones are also classified as phytoestrogens with weak estrogenic properties (Valachovicova et al., 2004). Interleukin-6 is a pleiotropic cytokine that plays a crucial role in immune physiology and is tightly controlled by hormonal-feedback mechanisms. Isoflavones modulate IL-6 gene-expression levels and may have therapeutical benefit in preventing cancer progression, aging discomforts, and restoring immune homeostasis (Dijsselbloem et al., 2004).

A systematic review of randomized clinical trials performed to evaluate the benefit of soy for the treatment of perimenopausal symptoms provides some evidence for the efficacy of soy preparations for perimenopausal symptoms, but the heterogeneity of the studies performed makes it difficult to achieve a definitive statement (Huntley and Ernst, 2004).

The ability of soybean extracts to inhibit mouse mammary adenocarcinoma tumor growth was not only due to the presence of genistein but to other constituents present (Hewitt and Singletary, 2003). Recent studies demonstrated a direct effect of soy saponins on cancer cells, which further leads to elucidating the nature of soy constituents involved in cancer protection (Kerwin, 2004).

The Bowman-Birk inhibitor, a serine protease inhibitor derived from soybeans, is presently being evaluated in clinical trials for its ability to serve as a cancer preventive or anti-inflammatory agent (Kennedy et al., 2002). Kunitz inhibitor was also found to inhibit cell invasiveness through suppression of urokinasetype plasminogen activator signaling cascade (Kobayashi et al., 2004).

Soy infant formulas are widely used, but only a few studies have evaluated their long-term safety or specific forms of toxicity, such as the effects of genistein and daidzein in soy infant formula, on the endocrine or immune systems. In addition, there is inconsistency in the existing data, which point to the need for more clinical and epidemiological studies (Chen and Rogan, 2004).

Soybean oil is the world's most widely used, edible oil. In the United States, soybean oil accounts for nearly 80 percent of edible-oil consumption. It contains 61 percent polyunsaturated fat and 24 percent monounsaturated fat. It is one of the few vegetable oils to contain linolenic acid, an omega-3 fatty acid (7.2 percent C18:3n-3) known to prevent cardiovascular diseases. Soybean oil also contains 54 percent C18:2n-6 linoleic acid, which is required for normal immune response (Meydani et al., 1991).

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Soy fibers

Due to its neutral taste and light color, soy fiber can be incorporated into a variety of high-fiber and reduced-calorie products, such as baked goods, cereal, and beverages. Clinical studies showed soy fiber provided all the benefits associated with both soluble and insoluble fiber. A soy-fiber-rich diet (6 percent) significantly lowered serum total cholesterol (TC), LDL-C, and atherosclerotic index, increased the ratio of HDL-L/TC, lowered serum fibrinogen (FB), platelet aggregation, and prolonged clotting time in rats (Wang et al., 1996). Lo et al. (1987) suggested a complementary role for soy fibers and soy protein in preventing atherosclerosis in rabbits. Bile acids were markedly lower in bran-soy treated females with cholelithiasis (Belonovskaia and Kliashtornaia, 1992).

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Soy protein

The U.S. Food and Drug Administration approved (1999) the association of soy proteins with coronary prevention. This claim was based on studies demonstrating that soyprotein components were primarily responsible for reducing cholesterolemia (Greaves et al., 1999; Sirtori et al., 1998; Nestel, 2002). Proteins appear to elicit the hypocholesterolemic response, mainly by activating liver LDL receptors (Baum et al., 1998), a mechanism tentatively attributed to specific protein components, i.e., the 7S globulin and its α - α' subunits (Lovati et al., 2000).

Plant-derived proteins, such as soy protein, were shown by Damasceno and coworkers (2000) to have a beneficial effect on atherosclerosis. Using a soy-protein isolate, they found a reduction in the level of oxidized LDL, as well as in the production of oxidized LDL antibodies, in rabbits.

Proteomic comparison of soy proteins used for clinical studies on hypercholesterolemia, particularly in Europe and the United States, indicate differences in the protein composition. These results may explain the variability found in experimental and clinical studies (Gianazza et al., 2003).

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Spearmint

Like peppermint, spearmint (*Mentha spicata*) is a popular food-flavoring agent and a valuable medicinal herb. The essential oil of spearmint was reported to have anti-bacterial (Imai et al., 2001) and antifungal (Soliman and Badeaa, 2002) activities, as well as anti-inflammatory activities, possibly through the suppression of neutrophil recruitment into the peritoneal cavity, as demonstrated in mice (Abe et al., 2004).

A water extract from spearmint inhibited the mutagenic activity of the parent compound, 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (IQ), in the presence of rat liver. These findings suggest that spearmint extract protects against IQ, and possibly other heterocyclic amines, through inhibition of carcinogen activation and via direct effects on the activated metabolite (Yu et al., 2004). Spearmint was also found as an effective chemopreventive agent that may suppress benzoyl peroxide-induced cutaneous oxidative stress, toxicity, and hyperproliferative effects in the skin of mice (Saleem et al., 2000).

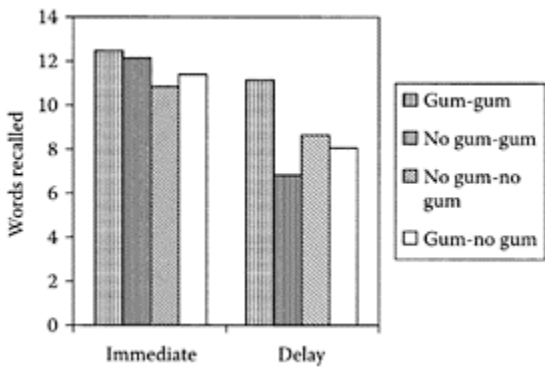


FIGURE S.94 Mean number of words recalled (maximum 15) after no

retention interval (“Immediate”) or after 24 h (“Delay”). Participants in two of the four groups chewed gum at initial learning (gum-gum, gum-no gum), and two of the groups chewed gum during both of the recall tests (gum-gum, no gum-gum). (From Baker et al., *Appetite*, 43:207–210, 2004. With permission.)

The constituents of anti-inflammatory and hemostatic active sites of *Mentha spicata* includes: ursane, 3-methoxy-4-methylbenzaldehyde, veratric acid, 5-hydroxy-3',4',6,7-tetramethoxyflavone, diosmetin, thymonin, and daucosterol (Zheng et al., 2002). Two monoterpenoid glycosides, spicatoside A and spicato-side B, were also isolated from whole herbs of *Mentha spicata* L. and found to have anti-inflammatory and hemostatic activities (Zheng et al., 2003). Recently, Akdogan et al. (2004) reported on lipid peroxidation and hepatic damage that occurs after *Mentha spicata* administration in rat liver and on nephrotoxic changes (Akdogan et al., 2003).

One of the major uses of spearmint is in chewing gum. A recent study by Baker et al. (2004) showed that chewing spearmint gum not only promoted initial learning but also led to context-dependent effects upon memory (Figure S.94). The same effects were also observed with sucking the gum.

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Spices

see also Individual spices Spices have been used for generations by humans as food and to treat ailments. Commonly used spices, such as garlic, black cumin, cloves, cinnamon, thyme, allspices, bay leaves, mustard, and rosemary, possess antimicrobial properties that, in some cases, can be used therapeutically. Other spices, such as saffron—a food colorant, turmeric—a yellow-colored spice, tea—either green or black—and flaxseed do contain potent phytochemicals, including carotenoids, curcumins, catechins, and lignan, respectively, which provide significant protection against cancer (Lai and Roy, 2004).

The improvement of food flavors was facilitated by the addition of different spices, such as garlic, red chili, and cloves. Subsequent research showed that it was the antioxidant activity of the spice extracts, due to the presence of high levels of antioxidants (Madsen and Bertelsen, 1995).

Spices have long been recognized for their digestive stimulant action. This action seems to be mediated by stimulating the liver to secrete bile rich in bile acids, components that are vital for fat digestion and absorption, and by stimulating enzymes that are responsible for digestion (reviewed by Platel and Srinivasan, 2004).

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Spinach

Spinach leaves, another good source of flavonoids (Goldbohm et al., 1998), contain other active components that exhibit antioxidative (Kuti and Konuru, 2004), antiproliferative (Sani et al., 2004), and anti-inflammatory (Lomnitski et al., 2000) activities. Spinach extracts have numerous beneficial effects, including chemo and central nervous system

A water-soluble antioxidant mixture isolated from spinach leaves contained both flavonoids and p-coumaric-acid derivatives (Bergman et al., 2001). It was found to be nonmutagenic and to show promising anticarcinogenic effects in experimental models, such as skin and prostate cancer (Lomnitski et al., 2003). Spinach is relatively rich in nitrogenous substances, hydrocarbons, and iron sesqui-oxide, which account for 3.3 percent of the total ash.

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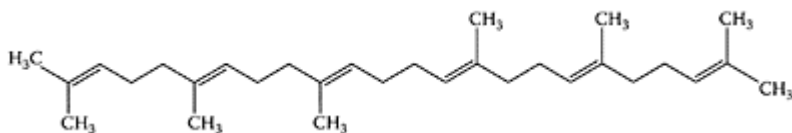
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Squalene

Squalene, a unique hydrocarbon, was first discovered in shark-liver oil in 1906 and named after the Latin root “squalus” (shark). It is a very potent antioxidant because of its six double bonds. Desai and coworkers (1996) showed squalene and a squalene-containing compound, Roindex, both partially prevented the development of chemical-induced cancer and to cause the regression of some of the existing tumors in a mouse-skin model. Dietary squalene was also found to lower plasma cholesterol because of its ability to downregulate HMG-CoA reductase, a key enzyme in cholesterol synthesis. Chan et al. (1996) reported that squalene enhanced the effect of pravastatin (a cholesterol-lowering drug) in patients over 20 weeks. The anticancer properties of squalene, particularly its ability to scavenge free radicals and oxygen-reactive species, was also demonstrated in skin subjected to radiation (Morliere et al., 1995). A study by O’Sullivan and coworkers (2002) showed it was squalene, not ω -3 fatty acids eicosapentaenoic (EPA) and docosapentaenoic (DHA) acids, that protected Chinese hamster V79 fibroblast cells from H₂O₂-induced DNA damage.

The effectiveness of squalene as an adjuvant was recently demonstrated by Suli et al. (2004), who showed it increased the immunogenic activity of nonpotentiated rabies vaccine by approximately 1.8-fold.

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St. John’s wort (*Hypericum perforation*)

see also Hyperforin and Hypericin Hypericin is a naturally occurring substance found in the common St. John’s wort that can also be synthesized from the anthraquinone

derivative emodin. It has been used traditionally throughout the history of folk medicine. In the last three



decades, St. John's wort has also become the subject of intensive biochemical research and is proving to be a multifunctional agent in drug and medicinal applications. Recent studies suggest it has antidepressive (Hirano et al., 2004; Zanolli, 2004; Muller et al., 2000), antineoplastic (Dona et al., 2004), antitumor (Gartner et al., 2004), and antiviral (human immunodeficiency and hepatitis C virus) properties (Jacobson et al., 2001; Kubin et al., 2005).

Hyperforins, a family of antimicrobial acylphloroglucinols, is thought to be a primary bioactive ingredient for antidepressive effects in the herb; and hypericins, a family of phototoxic anthraquinones, exhibits antimicrobial, antiviral, and antiherbivore properties *in vitro*, are two different classes of secondary metabolites produced by *Hypericum perforatum* L (Sirvent et al., 2003; Kirakosyan et al., 2004).

St. John's wort preparation has been used in large quantities in Germany for treating mild to moderate depression (Muller et al., 2000). Its efficacy has been demonstrated in several double-blind depression trials and some open-label studies with anxiety disorders. There is pharmacokinetic evidence for the serotonergic, dopaminergic, and GABA minergic activity of hypericum, all of which are implicated in social anxiety disorder (Hirano et al., 2004; Zanolli, 2004).

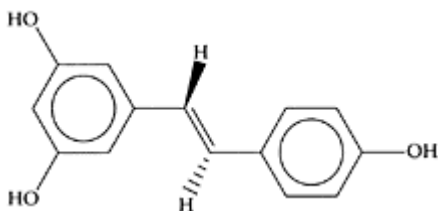
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Stilbenes

see also Resveratrol Stilbenes are nonflavonoid phenolics present primarily in grapes, berries, and wine products. Stilbenes are induced following stress, such as pathogenic attack and UV-C irradiation. One of the most extensively studied Stilbenes is trans-resveratrol (3,5,4'-trihydroxystilbene), whose health benefits (Granados-Soto, 2003) include antioxidant (Caruso et al., 2004), antimutagenic (Orsini and Verotta, 1999), anti-inflammatory (Donnelly et al., 2004), antiestrogenic (PozoGuisado et al., 2004), antiarrhythmic, and cardioprotective (Dong and Ren, 2004), as well as anticancer agent (Aggarwal et al., 2004; Kundu and Surh, 2004) properties.



Resveratrol. (From Li et al., *Free Rad. Biol. Med.*, 38:243–257, 2005. With permission.)

Cantos and coworkers (2002) used UV-C irradiation pulses to enhance the production of stilbenes in four grape varieties. Using this procedure, the total resveratrol content increased from 3.4-fold in Flame to 2315-fold in Red Globe. Using this method, the UV-C-irradiated grapes were considered a new functional food because of its enrichment with stilbenes.

Recently, several active stilbenes (piceatannol, 3,5,4'-trimethylpiceatannol, resveratrol, trimethylresveratrol) were reported to exhibit antiallergic activities. They

inhibited ionomycin-induced β -hexosaminidase release, suggesting that inhibition of $\text{Ca}(2+)$ influx or degranulation mechanisms after $\text{Ca}(2+)$ influx is important for their activities. Piceatannol, 3,5,4'-trimethylpiceatannol, resveratrol, and trimethylresveratrol also inhibited *in vitro* antigen-induced release of $\text{TNF-}\alpha$ and IL-4 significantly (Matsuda et al., 2004).

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Stinging nettle

The nettle tribe, *Urticaceae*, is spread throughout the world, with about 500 species, mainly tropical, though several, like the British species of stinging nettle, grows in temperate climates. The British species, belonging to the genus *Urtica* (the name derived

from the Latin, *uro*, to burn), are known for their well-armed leaves with stinging hairs with the burning properties fluid.

Water extract of stinging nettle has powerful antioxidant activity, evaluated using different antioxidant tests, including reducing power, free-radical scavenging, superoxide-anion-radical scavenging, hydrogen-peroxide scavenging, and metal-chelating activities. It also showed antimicrobial activity against nine microorganisms, antiulcer activity against ethanol-induced ulcerogenesis, and analgesic effect on acetic acid-induced stretching (Gulcin et al., 2004).

The long-term use of the stinging nettle leaf extract, an adjuvant remedy in rheumatic diseases dependent on a cytokine suppressive effect, was found effective in the prevention of chronic murine colitis. This effect seems to be due to a decrease in the Th1 response and may be a new therapeutic option for prolonging remission in inflammatory-bowel disease (Konrad et al., 2005). The clinical efficacy of stinging-nettle-leaf extracts in treatment of rheumatoid arthritis is explained by the ability of 13-hydroxyoctadecatrienic acid, one of the more active anti-inflammatory substances in stinging-nettle-leaf extracts, to suppress the expression of matrix metalloproteinases, which are known to have a role in inflammatory joint diseases (Schulze-Tanzil et al., 2002).

The antiproliferative effect of a methanolic extract of stinging-nettle roots on human prostatic epithelial and stromal cells was observed both in *in vivo* and in *in vitro* systems (Konrad et al., 2000). In animal models, the induced growth of prostatic lobe could be reduced by the polysaccharide fraction of the methanolic extract of stinging-nettle roots by 33.8 percent (Lichius et al., 1999). In many European countries, phytopharmaceuticals are commonly used for managing benign prostatic hyperplasia and associated lower urinary-tract symptoms, with these products representing up to 80 percent of all drugs prescribed for this disorder. Extracts from the fruits of saw palmetto and the roots of stinging nettle are particularly popular.

Although extracts from the stinging nettle may provide therapeutic value for some inflammatory medical conditions, it can also cause a wide range of cutaneous reactions. Contact with the hairs or spines on the stems and leaves of the stinging nettle causes the release of several biologically active substances that cause itching, dermatitis, and urticaria within moments of contact (Anderson et al., 2003).

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Strawberries

Strawberries are rich in ascorbic acid and a wide range of phenolic compounds. The significant inhibition by strawberry juice of the endogenous formation of *N*-nitrosoamino acids in humans could not be solely attributed to ascorbic acid (Hesler et al., 1992). Subsequent research showed that strawberries were high in antioxidant activity and capable of enhancing antioxidant capacity in humans (Wang et al., 1996; Cao et al., 1998). Strawberry supplementation in the diet of *N*-nitroso-methyl-benzylamine-treated rats reduced the multiplicity of esophageal tumors (Stoner et al., 1997). Ellagic acid was subsequently identified as one of the chemopreventive components present in strawberries, responsible for inhibiting cancers. It appears to prevent the binding of the reactive-carcinogenic components with DNA, as well as stimulate detoxification enzymes (Teel, 1986; Ahn et al., 1996). Treating Syrian hamster embryo (SHE) cells with the carcinogen benzo[*a*]pyrene for seven days, Xue and coworkers (2001) found that a methanolic extract from freeze-dried strawberries (*Fragara ananassa*) appeared to display chemopreventive activity by interfering with the uptake, activation, and detoxification of the carcinogen or by intervention of DNA binding and repair.

In strawberries, the most abundant bioactive compounds are ellagic acid and certain flavonoids: anthocyanin, catechin, quercetin, and kaempferol. These compounds in strawberries have potent antioxidant power, which helps to lower risk of cardiovascular events. Furthermore, strawberry extracts have been shown to inhibit COX enzymes *in vitro*, which would modulate the inflammatory process. Individual compounds in strawberries have demonstrated anticancer activity in several different experimental systems. Preliminary animal studies have indicated that diets rich in strawberries may also have the potential to provide benefits to the aging brain (Hannum, 2004).

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Sugar-beet fiber

Sugar-beet fiber, like wheat bran and flaxseed, is useful in the treatment of constipation, colon diverticulosis, and adiposity (Trepel, 2004). Rations containing sugar-beet pulp, given to broiler breeder females, were associated with higher water contents in the gastrointestinal tract, and it was proposed that this improved satiety and welfare (Hocking et al., 2004).

Mataumoto and coworkers (2001) showed that sugar-beet fiber reduced the ovariectomy-induced elevation in plasma cholesterol in 6-week-old ovariectomized female rats. Plasma total and non-HDL cholesterol were lowered significantly by 29 percent and 47 percent in rats fed sugar-beet fiber in comparison to the control diet.

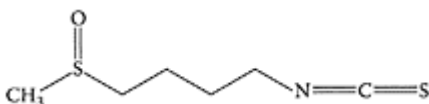
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Sulforaphane

Sulforaphane [1-isothiocyanto- (4R)-(methylsulfinyl) butane], an isothiocyante present naturally in widely consumed vegetables, has a particularly high concentration in broccoli. It was isolated from



Sulforaphane. (Adapted from Wu et al., *Mutat. Res.*, 589:81–102, 2005.)

SAGA broccoli as the major phase II enzyme inducer, present in organic solvent extracts of this vegetable (Zhang et al., 1994). Sulforaphane was found to block chemical-initiated tumor formation in rats (Faulkner et al., 1998). The effectiveness of sulforaphane is based on induction of hepatic detoxifying enzymes. Sulforaphane is a very potent inducer of phase II enzymes, UDP-glucuronosyltransferase 1A1, and glutathione *S*-transferase A1 (Bacon et al., 2003). It was shown to inhibit cytochrome P-450 (CYP2E1) involved in the activation of a variety of carcinogens (Barcelo et al., 1996; Faulkner et al., 1998).

Recent studies report that induction of thioredoxin reductase by sulforaphane is mediated by putative antioxidant response elements found in the promoter similar to the upregulating mechanism of other antioxidant enzymes (Hintze et al., 2003). In highly proliferative HT29 cells, sulforaphane induces a cell-cycle arrest, followed by cell death caused by a proapoptotic protein bax-dependent pathway. These results suggest that in addition to the activation of detoxifying enzyme activities, specific mechanisms, such as apoptosis, are also involved in the sulforaphane-associated chemoprevention of cancer (Gamet-Payraastre et al., 2000; Misiewicz et al., 2004). Similar results were found in leukemic cells (Fimognari et al., 2002) and human melanoma cells (Misiewicz et al., 2003) with recent reports suggesting sulforaphane can halt human breast-cancer cells (Johnston, 2004). Animal studies demonstrated that sulforaphane significantly reduces the formation of total and multicrypt foci in azoxymethane-induced colonic aberrant crypt foci F344 rats, during both the initiation phase and the postinitiation treatment, indicative of its potential to prevent colon cancer (Chung et al., 2000). Recent studies demonstrated the potential of sulforaphane for treating pancreatic cancer (Pham et al., 2004). Jackson and Singletary (2004) reported sulforaphane was an effective inhibitor of human mcf-7 mammary-cancer cells.

A potent decrease in lipopolysaccharide-induced secretion of proinflammatory and procarcinogenic signaling factors (i.e., NO, prostaglandin E₂, and tumor-necrosis factor)

in cultured Raw 264.7 macrophages after sulforaphane treatment suggested that anti-inflammatory mechanisms contribute to sulforaphane-mediated cancer chemoprevention (Heiss et al., 2001).

Sulforaphane was also shown to be a potent bactericidal agent against both extracellular and intracellular *H. pylori* *in vitro*. Haristoy et al. (2003) investigated the efficacy of sulforaphane *in vivo* against *H. pylori* by using a recently developed model, which uses human gastric xenografts in nude mice. They observed that *H. pylori* can be eradicated from human gastric xenografts after a short-term administration of sulforaphane at a dose that can be achieved in the human diet. Thus, sulforaphane delivered in the diet could be beneficial for the treatment of *H. pylori*-associated gastric diseases.

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Summer savory (*Satureja hortensis*)

Satureja hortensis L. (Lamiaceae) is an annual herb, traditionally used in the Eastern Anatolia region of Turkey as folk medicine for treatment of different infectious diseases and disorders. In Iranian folk medicine, it was used as muscle and bone-pain reliever.

Uslu and coworkers (2003) showed that the activity of nitric-oxide synthase enzyme, and concentration of nitric-oxide metabolites were both significantly reduced by topical administration of *S. hortensis* extract. Histological examination demonstrated reduced inflammation. Thus, their data suggest that *S. hortensis* extract may have the potential as an antiinflammation agent in the treatment of rhinosinusitis diseases. Antimicrobial test results showed that the essential oil of *S. hortensis* had great potential in antimicrobial activities against different bacteria, fungi, and yeast species. Thymol (29.0 percent), carvacrol (26.5 percent), γ -terpinene (22.6 percent), and p-cymene (9.3 percent) were the main components in essential oil of *S. hortensis* (Gulluce et al., 2003).

The essential oil of *S. hortensis* was also found as a relaxant of rat-isolated ileum. In addition to antispasmodic activity *in vitro*, it inhibited castor oil-induced diarrhea in mice. Thus, *S. hortensis* essential oil may have clinical benefits for treatment of some gastrointestinal disorders (Hajhashemi et al., 2000).

The polyphenolic fraction and the essential oil of *S. hortensis* L. were both shown to have antinociceptive and anti-inflammatory effects (Hajhashemi et al., 2002). The antioxidant capacities and total phenol content were demonstrated in the ethanol and acetone extracts of the dried material from a number of sources, including summer savory (Exarchou et al., 2002).

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Sunflower

see Sunflower oil and Sunflower seed protein

Sunflower oil

Alpaslan and Gunduz (2000) showed that growing conditions significantly affected the fatty-acid compositions of sunflower varieties. In the 1991 and 1992 crop years, they ranged for oil content 44.2–51.2 percent (on dry weight basis) and 43.0–51.5 percent (on dry weight basis); oleic acid 14.8–18.5 percent and 32.9–40.1 percent; linoleic acid 69.5–74.5 percent and 49.7–55.7 percent; and tocopherol content (as α -tocopherol) 648–860 mg/kg and 524–880 mg/kg, respectively.

A significantly higher LDL susceptibility to oxidation was observed after sunflower-oil intake in comparison with virgin olive oil, in spite of an increase in LDL α -tocopherol concentration in the sunflower-oil group. These results provide further evidence that sunfloweroil-enriched diets do not protect LDL against oxidation, as virgin olive oil does, in patients with peripheral vascular disease (Aguilera et al., 2004).

In comparison to other commercially available antimicrobial agents, ozonized sunflower oil demonstrated significant antimicrobial activity and anti-inflammatory and wound-healing properties (Rodrigues et al., 2004). Treatment of preterm infants <34 weeks in Egypt with sunflower-seed oil resulted in a significant improvement in skin condition and a highly significant reduction in the incidence of nosocomial infections compared with infants not receiving topical prophylaxis. This study suggests the potential of topical therapy to reduce infections and save newborn lives in developing countries (Darmstadt et al., 2004).

Sesame oil and sunflower oil offered 20 percent and 40 percent protection, respectively, in mouse-skin tumor model. The antioxidant capabilities of these compounds could not solely explain the observed anticancer characteristics. Thus, the observed chemopreventive effects warrant more attention, since they already exist in the population with no known adverse effects (Kapadia et al., 2002).

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TABLE S.62

Lipid Concentrations (10^{-2}kgm^{-3}) in Plasma of Rats Fed Casein and Sunflower-Seed Protein Fraction (PF).

	Total Cholesterol	Triglyceride	MDL Choles terol	VLDL Chole sterol	LDL Chole sterol	LDL Cholesterol/ HDL Cholesterol	Total Cholesterol/ HDL Cholesterol
Casein	53.9±5.4	73.8±3.5	9.3±1.6	14.8±2.2	29.9±4.8	3.1±0.4	5.8±0.5
PF	37.2±3.2*	60.0±3.7**	5.5±1.4***	12.0±0.8	19.7±3.4	3.6±1.5	6.8±0.6

Values are mean ±SEM, n=8, HDL, high-density lipoprotein, LDL-low-density lipoprotein, VLDL-very-low-density lipoprotein. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Source: From Sen and Bhattacharyya, *J. Sci. Food Agric.*, 81:347–352, 2000. With permission.

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Sunflower-seed protein

In addition to oil, sunflower also produces a protein. Over the past few decades, evidence has accrued that ingestion of plant proteins lowers plasma cholesterol in animals (Carroll, 1995). One mechanism suggests that plant proteins suppress the intestinal absorption or reabsorption of neutral lipids, reducing the cholesterol pool within the body (Van Deer

Meer and Beynen, 1987). Sen and Bhattacharyya (2000) enzymatically extracted dehulled sunflower seeds with pectinase to produce a protein-rich fraction low in fiber and chlorogenic acid. The protein-rich fraction significantly reduced plasma cholesterol ($p<0.02$) and triglyceride ($p<0.02$) in rats fed the sunflower-seed protein fraction compared to casein (Table S.62). While the HDL-cholesterol levels were significantly reduced by the sunflower-seed protein fraction, the total cholesterol/HDL cholesterol and LDL cholesterol/HDL cholesterol ratios were not significantly different. Thus, the sunflower-seed protein fraction exhibited similar hypolipidemic effects to casein.

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Sweet basil

Basil or sweet basil (*Ocimum basilicum*) is cultivated throughout India. It is rich in essential oils that have been the subject of numerous chemical studies (Grayer et al., 1996). Sweet basil was grown by local people as a medicinal plant, culinary herb, and antimicrobial agent. Some 30 monoterpenoids, sesquiterpenoids, and phenylpropanoids identified in basil oil as the major components (more than 20 percent of the total essential-oil composition) were linalool, methyl chavicol, eugenol, methyl eugenol, and geraniol (Grayer et al., 1996).

Basil essential oils and their principal constituents were found to exhibit antimicrobial activity against a wide range of Gram-negative and Gram-positive bacteria, yeast, and mold (Suppakul et al., 2003). Linalool alone showed a moderate antifungal activity, while eugenol showed no activity at all. Mixing the two components in a ratio similar to their concentrations in the original oil was found to enhance the antifungal properties of basil oil, indicating a synergistic effect (Edris and Farrag, 2003).

The major antioxidant compound in the methanolic extract of sweet basil was confirmed as rosmarinic acid. The results showed that one rosmarinic acid can capture 1.52 radicals, and, furthermore, the existence of a synergistic effect between α -tocopherol and rosmarinic acid was revealed (Jayasinghe et al., 2003).

The effects of an alcoholic extract of the fresh leaves of sweet basil on Swiss albino mice were increasing the activity of xenobiotic metabolizing phase I and phase II enzymes, elevating antioxidant-enzyme response by increasing significantly the hepatic glutathione reductase, superoxide dismutase, and catalase activities, increasing glutathione content, and decreasing lipid peroxidation and lactate dehydrogenase activity

in the liver after eight to nine weeks. Furthermore, chemopreventive response was evident from the reduced tumor, as well as from the reduced percentage of tumor-bearing animals (Dasgupta et al., 2004).

Recently Fang and coworkers (2004) reported that essential oil from sweet basil can act as skin-permeation enhancers to promote the percutaneous absorption of drugs. This might be mainly due to improvement in the partitioning of the drugs to the stratum corneum.

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Sweet flag (*Acorus calamus*)

Sweet flag (*Acorus calamus* L.) is a perennial shrub that grows in damp, marshy places in India, North America, and Europe. The rhizomes of *Acorus calamus* are empirically used for treating a wide variety of human diseases. It is recognized as an Indian drug with antibacterial, anticonvulsant, antiveratrinic, and antiarrhythmic action (Madan et al., 1960), as well as a tranquilizing agent (Menon and Dandiya, 1967).

The ethanol extract of *Acorus calamus* rhizomes exhibited a large number of actions on the CNS similar to α -asarone (an active principle of *A. calamus*) but differed from the latter in several other respects. These differences could be due to the effects of other chemicals in the plant extract (Vohora et al., 1990). The alcoholic extract also antagonized spontaneous motor activity and also amphetamine-induced hyperactivity in mice. It was less potent than chlorpromazine, but still exerted sedative and tranquilizing action (Panchal et al., 1989).

Neurobehavioral changes produced by acrylamide could be prevented following treatment with *Acorus calamus* rhizomes (Shukla et al., 2002). Administration of a 50

percent ethanolic extract (100 and 200 mg/kg), as well as saponins (10 mg/kg) isolated from the extract showed significant hypolipidemic activity (Parab and Mengi, 2002). Recently, Mehrotra and coworkers (2003) demonstrated the anti-proliferative and immunosuppressive potential of an ethanolic extract from *Acorus calamus* *in vitro*.

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Sweet potatoes

Sweet potatoes, a crop native to South America, are easy to grow and have become a staple food in many African countries. The orange-fleshed sweet-potato variety is rich in β -carotene, which offers hope to the population who are currently beyond the reach of a vitamin A supplement. The effect of 60 days of daily supplementation with 750 mg retinol equivalents (RE) of pureed sweet potatoes were tested by Haskell et al. (2004). The overall geometric mean of initial vitamin A stores was 0.108 \pm 0.067 mmol. Relative to the low vitamin A control group, the estimated mean changes in vitamin A stores were 0.029 mmol. Vitamin A equivalency factors (β -carotene :retinol, wt:wt) were estimated as approximately 13:1 for sweet potato. Thus, daily consumption of pureed sweet potatoes has a positive effect on vitamin A stores in populations at risk of vitamin A deficiency (Haskell et al., 2004).

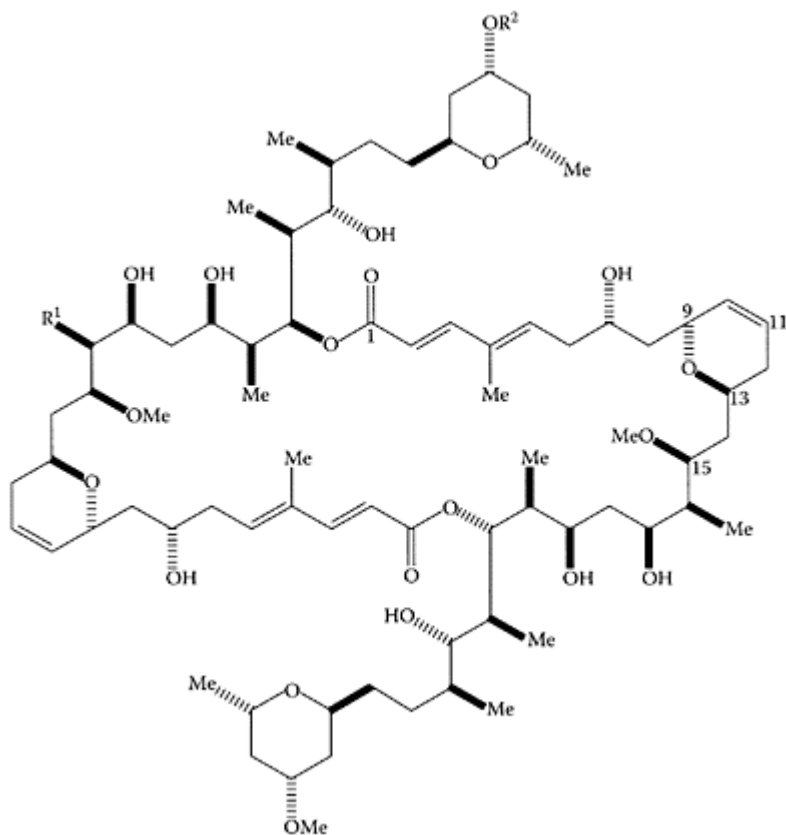
The major phenolic components contained in the 70 percent methanol extract of sweet potatoes with strong antioxidative activity were identified as chlorogenic acid and isochlorogenic acid-1, -2, and -3. The other minor free phenolics were identified as caffeic acid and 4-*O*-caffeoylquinic acid. Chlorogenic acid and isochlorogenic acids, however, had only a slight antioxidative activity. Thus, the effective antioxidant activity

of the sweet-potato extract was proposed to be mainly based on the synergistic effect of phenolic compounds with amino acids (Hayase and Kato, 1984). The dietary fiber content of sweet potatoes was found to range from 9–12 percent for cured roots. Soluble and insoluble dietary fiber averaged 5–30 percent and 543 percent, respectively (Mullin et al., 1994).

Anthocyanins are the chemical components that give the intense color to sweet potatoes, as in many other fruits and vegetables. Epidemiological investigations have indicated that moderate consumption of anthocyanin products is associated with a lower risk of cardiovascular disease and improvement of visual functions (Hou, 2003). Recently, the leaves of sweet potatoes were found to be rich in nutritive and functional components. They were found to contain a large amount of protein, showing high aminoacid score, soluble dietary fibers and minerals, particularly iron, and vitamins, such as carotene, vitamin B₂, vitamin C, and vitamin E. Further-more, polyphenol content in the leaves was comparatively high. These results suggest that the whole parts of sweet potatoes should be utilized as valuable foodstuffs (Ishida et al., 2000).

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Swinholide A (1): $n=1$, $R^1=R^2=Me$

Swinholide B (2): $n=1$, $R^1=H$, $R^2=Me$

Swinholide C (3): $n=1$, $R^1=Me$, $R^2=H$

Swinholides A, B, and C. (From Hayakawa and Miyashita, *Tetrahedron Lett.*, 41:707–711, 2000. With permission.)

Swinholide

The marine natural products swinholides A (**1**), B (**2**), and C (**3**), 44-membered dimeric macrolides isolated from the Okinawan marine sponge *Theonella swinhoei* (Carmely and Cashman, 1985), have been shown to exhibit potent cytotoxicity against a variety of human carcinoma-cell lines, as well as a broad spectrum of antifungal activity (Tanaka et al., 1990; Doi et al., 1991). Their structures are characterized by the C_2 -symmetrical dimeric macrolides in which two polypropionate-derived chains take axial orientation on a tetrahydropyran ring. Their unique structures and potent anticancer activities have

elicited much attention from synthetic organic chemists toward the synthesis of polypropionate-derived bioactive compounds (Paterson et al., 1994; Hiroyuki and Masaaki, 2000).

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Symbiotic

see also Prebiotics and Probiotics Prebiotics, usually polysaccharides, exhibit strong bioactivity, and the ingestion of prebiotics has been shown to reduce the rate of infection and restore health in sick and postoperative patients. Probiotics are bacteria that reduce or eliminate potentially pathogenic microorganisms, as well as various toxins, mutagens, and carcinogens. They modulate the innate and adaptive immune defense mechanisms, promote apoptosis, and release many nutrients, antioxidants, growth, coagulation, and other factors necessary for recovery. A combination of prebiotics and probiotics is referred to as “synbiotics” if it has a stronger effect on intestinal diseases than probiotics or prebiotics alone (Holmes, 2003; Tuohy et al., 2003).

Synbiotics treatment was also found to contribute in the treatment of severe acute pancreatitis, chronic hepatitis, and liver transplantation (Bengmark, 2003). It was also reported as an alternative to lactulose for the management of minimal hepatic encephalopathy in patients with cirrhosis (Liu et al., 2004).

Roller and coworkers (2004) demonstrated that synbiotic supplementation in carcinogentreated rats primarily modulated immune functions in the Peyer’s patches, with a reduction in the number of colon tumors. Other evidence for the cancer-preventing properties of probiotics and prebiotics is derived from studies on fecalenzyme activities in animals and humans, inhibition of genotoxicity of known carcinogens *in vitro* and *in vivo*, suppression of carcinogeninduced preneoplastic lesions and tumors in laboratory animals. Some of these studies indicate that combinations of probiotics and prebiotics are more effective than either one of these treatments (Burns and Rowland, 2000).

Synbiotic treatment to short-bowel patients with refractory enterocolitis was very promising. It improved the intestinal bacterial flora, increased short-chain fatty acids in the feces, and accelerated their body-weight gain (Kanamori et al., 2004). Oral supplements with synbiotic also increased energy intake and promoted weight gain in acutely ill children receiving antibiotics (Schrezenmeir et al., 2004).

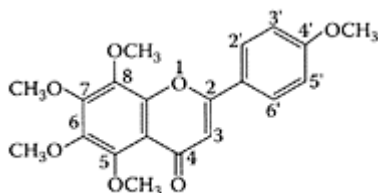
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T

Tangeretin

Tangeretin is a flavone derivative (5,6,7,8,4'-pentamethoxyflavone) present in citrus-fruit peel. Pan and coworkers (2002) showed that it induces cell-cycle G_1 arrest in colorectal carcinoma COLO 205 cells. Exposure of cells to tangeretin resulted in inhibition



Tangeretin

(From Nielsen et al., *Food Chem. Toxicol.*, 38:739–746, 2000. With permission.)

of cyclin-dependent kinases 2 and 4 in a dose-dependent manner. Tangeretin also increased the level of Cdk inhibitor p21 and p27 protein. These studies showed that the growth inhibition was mediated by inhibiting the activities of cyclin-dependent kinases 2 and 4.

The modulation of apoB-containing lipoprotein metabolism by tangeretin was studied by Kurowska and coworkers (2004). A 24-h exposure of human hepatoma-cell line HepG2 to tangeretin decreased intracellular synthesis of cholesteryl esters, free cholesterol, and TAG, which were associated with decreased activities of DAG acyltransferase and microsomal triglyceride transfer protein. Tangeretin was also found to activate the peroxisome proliferator-activated receptor, a transcription factor with a positive regulatory impact on fatty acid oxidation and TAG availability. Tangeretin was also reported to upregulate the function of the E-cadherin/catenin complex in human breast carcinoma cells. This leads to firm cell-cell adhesion and inhibition of invasion *in vitro*.

The neuroprotective effects of tangeretin, found to cross the blood-brain barrier, were elucidated in the 6-hydroxydopamine lesion rat model of Parkinson's disease (Datla et al., 2001).

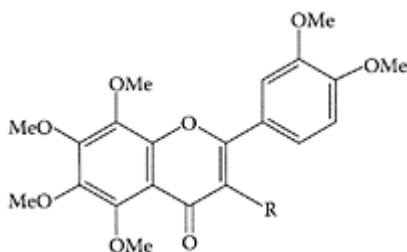
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Tangerine

see also Tangeretin Tangerine is a member of the citrus family. In addition to vitamin C, it contains polymethoxylated flavones, such as tangeretin and nobiletin, found mainly in the peels of tangerines and oranges and in smaller amounts in the juices of these fruits. These flavones were shown to have cholesterol- and triacylglycerol-lowering potential (Kurowska and Manthey, 2004). Tangerines are also a rich source for β -carotene, folate, and potassium. Like other citrus fruits, tangerines contain d-limonene, another flavonoid.

Citrus nobiletin, a polymethoxylated flavone found in tangerine peels, was found to exhibit



Nobiletin. (From Iwase et al., *Cancer Lett.*, 163:7–9, 2001. With permission.)

chemopreventive ability against azoxymethane-induced rat colon carcinogenesis (Suzuki et al., 2004). β -Cryptoxanthin, a major source of vitamin A, is often second only to β -carotene in tangerines. Increasing amounts of free β -cryptoxanthin were detected in chylomicrons and serum of subjects following ingestion of tangerine juice (Wingerath et al., 1995). Subjects that frequently ($\geq 3/d$) consumed tropical fruits with at least 50

mg/100 g β -cryptoxanthin, such as papaya and tangerine, had twofold the plasma β -cryptoxanthin concentrations of those with intakes of <4/wk (Irwig et al., 2002).

Jian and coworkers (2005) showed that an intake of citrus fruits was inversely associated with prostate-cancer risk. This risk declined with increasing consumption of α -carotene, β -carotene, β -cryptoxanthin, lutein, and zeaxanthin, all found in the tangerine. Previous work by Guo et al. (2000) isolated and identified hesperidin, neohesperidin, nobiletin, and tangeritin in tangerine peel.

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Taraxacum platycarpum

Taraxacum platycarpum is a Chinese herb used in traditional Oriental medicine. The extracts from this herb have anti-inflammatory properties used for treating ulcers and colitis. Yun and coworkers (2002) isolated and characterized an anticoagulant from *T. platycarpum*. It appeared to be a protein monomer with a molecular weight of 31–33 kDa. The anticoagulant properties included delaying thrombin time and prothrombin time and activating partial-thromboplastin time. In addition, it activated murine macrophages to produce cyclooxygenase-2 and nitricoxide synthase, as well as the secretion of tumor necrosis factor.

A polysaccharide fraction from *T. platycarpum* showed potent immunopotentiating activities, with antitumor activities. It inhibited the growth of solid tumor and increased

peritoneal exudate cells and immunoorgan weights in normal mice, as well as increased hypersensitivities in tumor-bearing mice (Jeong et al., 1991).

Desacetylmatricarin was identified as the active principle responsible for the antiallergic property of *T.platycarpum* (Cheong et al., 1998).

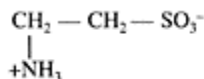
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Taurine

Taurine is a conditionally essential

amino acid that has been shown to be involved in certain aspects of mammalian development (Sturman, 1993). The molecule contains a sulfonic-acid group, rather than the carboxylic



acid moiety, that is not incorporated into proteins and is one of the most abundant free amino acids in many tissues, including skeletal and cardiac muscle and the brain (Huxtable, 1992). *In vitro* and animal studies demonstrated that low levels of taurine are associated with various pathological lesions, including cardiovascular disorders (Satoh and Sperelakis, 1998; Oudit et al., 2004), retinal degeneration (Sheik et al., 1981), and growth retardation (Geggel et al., 1985). Taurine is also involved in such metabolic activities as bile-acid conjugation (Smith et al., 1991; Carrasco et al., 1990), detoxification (Waterfield et al., 1993; Timbrell and Waterfield, 1996) membrane stabilization (Qi et al., 1995), osmoregulation (Olivero and Stutzin, 2004), and modulation of cellular calcium levels (Satoh and Sperelakis, 1998). Clinically, taurine has been used in the treatment of cardiovascular diseases (Azuma et al., 1992; Modi and Suleiman, 2004), ischemia-reperfusion injury (Kingston et al., 2004), hypercholesterolemia (Matsushima et al., 2003), epilepsy and other seizure disorders (Airaksinen et al., 1980), macular degeneration (Sturman, 1986), Alzheimer's disease (Csernansky et al., 1996), hepatic disorders (Matsuyama et al., 1983), alcoholism, and cystic fibrosis (Smith et al., 1991; Carrasco et al., 1990).

Taurine was recently shown by Takatani and coworkers (2004) to inhibit ischemia-induced apoptosis in cultured neonatal rat cardiomyocytes by increasing the activities of Akt kinase and inactivating caspase-9. Figure T.95A shows simulated ischemia induced a 4.5-fold and 11-fold increase in caspase-9 and caspase-3 compared to the control. In the presence of taurine caspase-9 and caspase-3, activities were significantly reduced. Thus, taurine treatment could be beneficial for treating heart failure.

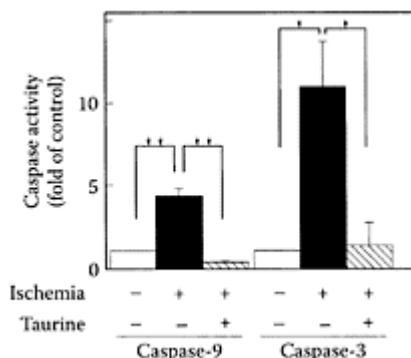


FIGURE T.95 Taurine prevents ischemia-induced caspase-9 and caspase-3 processing in cultured cardiomyocytes. Cardiomyocytes were exposed to ischemia for 30 h in the absence (-) or in the presence (+) of 20 mM taurine. (From Takatani et al., *Biochem. Biophys. Res. Commun.*, 316:484–489, 2004. With permission.)

Recent *in vivo* and *in vitro* evidence found that taurine, through its ability to control sarcolemmal excitability and muscle contractibility, could have beneficial effects in many muscle dysfunctions (Conte Camerino et al., 2004).

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Tea

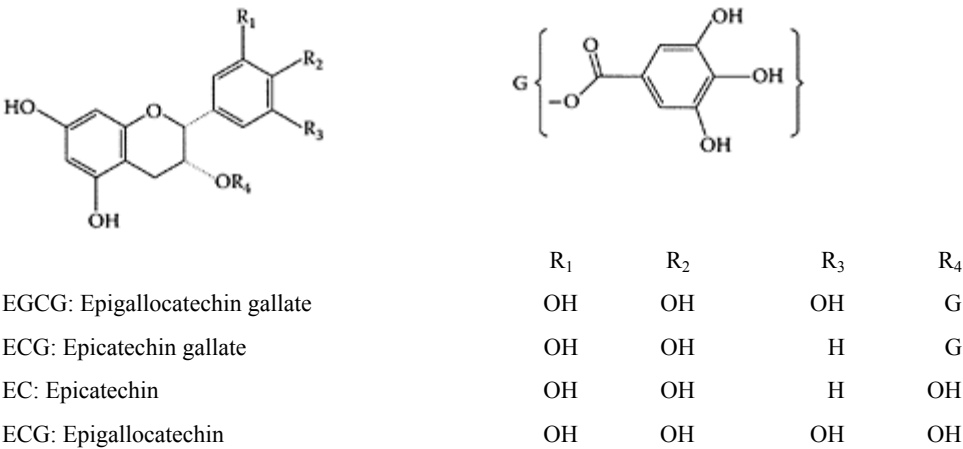
see also Black, Green, Oolong, and Rooibos tea Tea is the most-consumed drink in the world after water. Green, black, and oolong teas are the three major commercial types of teas and differ in how they are produced and in their chemical composition. Green tea is prepared by pan-frying or steaming fresh leaves to heat-inactivate oxidative enzymes and then the leaves are dried. By contrast, black tea is produced by crushing fresh tea leaves

and allowing enzyme-mediated oxidation to occur. Green tea is chemically characterized by the presence of large amounts of polyphenolic compounds, known as catechins (Balentine et al., 1997). These include epicatechin, epigallocatechin, epicatechin-3-gallate, epigallocatechin-3-gallate (EGCG), caffeine, and theanine (Scheme T.58).

An accumulated number of population studies suggest that consumption of green- and black-tea beverages may have positive health benefits (Peters et al., 2001; Blumberg, 2003). Tea is an important source of flavonoids in the diet, with levels approaching 200 mg/cup for a typical brew of black tea (Lakenbrink et al., 2001). Tea flavonoids are potent antioxidants that are absorbed from the gut, leading to a significant increase in the antioxidant capacity of the blood. Beneficial effects of increased antioxidant capacity in the body include the reduction of oxidative damage to important biomolecules. The scientific support is strongest for the protection of DNA from oxidative damage after black- or green-tea consumption (Rietveld and Wiseman, 2003). The beneficial effect of tea on the cardiovascular system has been clearly established (Kris-Etherton et al., 2002). One mechanism is that it improves the vascular endothelium, which is known to play a central role in the regulation of vascular homeostasis, and that endothelial dysfunction contributes to the pathogenesis and clinical expression of cardiovascular disease (Vita, 2003).

As a source rich with antioxidants, tea is also involved in protection against the development of cancer (Kris-Etherton et al., 2002) and neurodegenerative diseases (Kakuda, 2002). Tea polyphenols seem able to modulate cell growth by arresting the cell cycle or inducing apoptosis. In addition, administration of green tea reduced the levels of 8-OHdG in the lung DNA. Other studies have also shown green tea inhibited the activity of phase I enzymes and induced phase II enzymes. Together, these mechanisms may be responsible for the protective effects of tea against carcinogenesis (Chung et al., 2003; Lambert and Yang, 2003).

Studies with human cancer-cell lines have demonstrated that epigallocatechin-3-gallate (EGCG), one of the major tea polyphenols, may be involved in its protective activities. It inhibits mitogen-activated protein kinases, cyclindependent kinases, growth factor-related cell signaling, activation of activator protein 1 (AP-1),



SCHEME T.58 Structures of major polyphenols in green tea. (From Ghosh et al., *Biochem. Biophys. Res. Commun.*, 325:807–811, 2004. With permission.)

and nuclear factor κ B (NF- κ B), topoisomerase I, and matrix metalloproteinases, as well as other potential targets (Lambert and Yang, 2003).

References

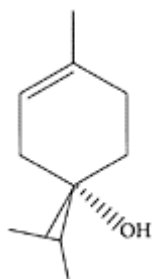
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Tea tree (*Melaleuca alternifolia*)

Melaleuca alternifolia is a tea tree native to Australia. The oil obtained by steam distillation of its leaves was reported to have antibacterial, antifungal, antiviral, anti-inflammatory, and analgesic properties (Carson et al. 1998; Messenger et al., 2005).

Currently, tea-tree oil is used in cosmetics, health-care products, and as an effective antiseptic (Williams et al., 1997). The concentrations of tea-tree oil found in commercially available products range from 2 percent to 5 percent. Terpinen-4-ol is the main antimicrobial component but other components, such as α -terpineol, also have antimicrobial activities similar to those of terpinen-4-ol (Carson and Riley, 1995). Studies on the antifungal mechanism of tea-tree oil and its components against *Candida albicans*, *Candida glabrata*, and *Saccharomyces cerevisiae* was due to the alteration in membrane properties and compromising membrane-associated functions (Hammer et al., 2004). The main antioxidants identified in tea-tree oil are α -terpinene, α -terpinolene, and γ -terpinene (Kim et al., 2004).

Recently, tea-tree oil was found to be effective as an adjunctive therapy in treating osteomyelitis and infected chronic wounds in case studies and small clinical trials (Halcon and Milkus, 2004).



Terpinen-4-ol. (From Biju et al., *J. Pharmaceut. Biomed. Anal.*, 38:41–44, 2005. With permission.)

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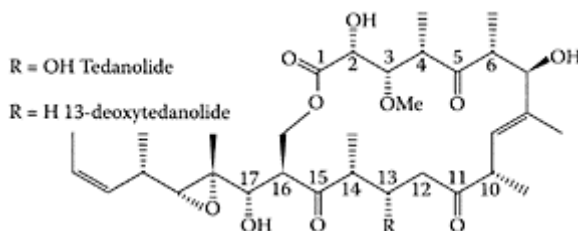
Tedanolide

Tedanolide is a novel macrolide, isolated from the abundant Caribbean sponge, *Tedania ignis* (fire sponge). It was first reported by Schmitz and coworkers in 1984 to be a potent marine antitumor agent (Schmitz et al., 1983). A closely related compound, 13-deoxytedanolide, was reported by Fusetani et al. (1991) in the Japanese sponge, *Mycale adhaerens*. *In vitro* studies revealed that tedanolide possessed an ED₅₀ of 0.25 ng/mL and 1.6 pg/mL in KB and PS cells, respectively, causing cell accumulation in the S phase of the cell cycle at concentrations as low as 0.01 µg/mL (Schmitz et al., 1984). Similarly, 13-deoxytedanolide expressed an IC₅₀ of 94 pg/mL against P388 murine leukemia cells (Fusetani et al., 1991).

Tedanolide increased the life span of mice implanted with lymphocytic leukemia by 23 percent when given 1.5 µg/kg of body weight (Schmitz et al., 1988). No information, however, is available on the biochemical mechanism of action of the tedanolides. A synthetic strategy for constructing potent marine antitumor agents, tedanolide and 13-deoxytedanolide, was recently described (Smith et al., 2004; Roush and Newcom, 2002).

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Tedanolide and 13-deoxytedanolide. (From Taylor et al., *Tetrahedron Lett.*, 39:9361–9364, 1998. With permission.)

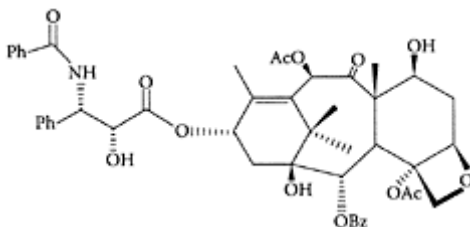
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Terpenes

see also Monoterpenes Terpenes are organic solvents, usually derived from natural sources, such as pine trees or citrus fruit, mainly as constituents of essential oils. Generally, they have strong, characteristic odors. Many terpenes are hydrocarbons, but oxygen-containing compounds, such as alcohols, aldehydes, or ketones (*terpenoids*) are also found. Their building block is the hydrocarbon isoprene, $\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$. Terpene hydrocarbons have a molecular formula of $(\text{C}_5\text{H}_8)_n$. They are volatile, organic compounds that are flammable or combustible.

In vitro and *in vivo* studies demonstrated terpenes had antibacterial (Alma et al., 2004), antifungal (Inoue et al., 2004), and anticancer activities. Specific terpenes used in cleaning are pinene, *d*-limonene, and turpentine. Menthol, a monoterpene (10 carbons) isolated from various mints, is a topical pain reliever and anti-puritic (Wasner et al., 2004). Borneol, a monoterpene derived from pine oil, is used as a disinfectant and deodorant. Camphor is another monoterpene used as a counterirritant (Taniguchi et al., 1994), anesthetic (Kuroda et al., 2004), expectorant, and antipruritic (Shunying et al., 2005). Recently, serious pediatric toxicity resulting from exposure to small amounts of camphor-containing products were reported (Love et al., 2004).

One of the most well-known, medicinally valuable terpenes is the diterpene, taxol. It was first isolated from the bark of the Pacific yew, *Taxus brevifolia*, in the early 1960s, but its value as an anticancer drug was not determined until the late 1980s (Beijnen et al., 1994).



Taxol. (Adapted from Huang et al., *Bioorg. Med. Chem.*, 9:2237–2242, 2001.)

Taxol is thought to induce apoptosis through the release of cytochrome C and activation of caspases. However, the effect of taxol on dendritic cells was shown by Joo et al. (2003) to induce immunosuppression in patients with cancer by inhibition of dendritic cells-activated T cell proliferation. The effect of taxol on dendritic cells includes induction of immunosuppression in patients with cancer by inhibition of dendritic cells-activated T-cell proliferation (Joo et al., 2003).

Other examples of monoterpenes are nerol and citral, while sesquiterpenes include nerolidol and farnesol. An example of a diterpene is phytol, while squalene and carotene are examples of a triterpene and a tetraterpene, respectively.

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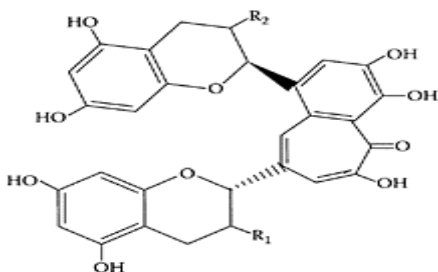
Theaflavins

Theaflavins (TFs) are specific, higher-molecular-weight polyphenol compounds arising from enzymatic oxidation (Scheme T.59). All phenolic compounds are highly unstable and are rapidly transformed into various reaction products when the plant cells are damaged (for instance, during food processing).

TFs are pigments found in both black and oolong teas. They are formed from polymerization of catechins at the fermentation or semifermentation stage during the manufacture of black or oolong tea (Subramanian et al., 1999). TFs contribute to the characteristic bright orange-red color of black tea. The major TF in black and oolong teas are theaflavin (TF1), theaflavin-3-gallate (TF₂A), theaflavin-3'-gallate (TF₂B), and theaflavin-3,3'-digallate (TF₃). TFs have recently received much attention as protective agents against cardiovascular disease and cancer (Buschman, 1998; Yang, 1999; Boone et al., 2000). They are also believed to have a wide range of other pharmaceutical benefits, including antihypertensive (Henry and Stephens-Larson, 1984; Hara et al., 1987), anti-oxidative (Halder and Bhaduri, 1998; Leung et al., 2001), and hypolipidemic (Chan et al., 1999) activities.

Leung and coworkers (2001) demonstrated that TFs present in black tea possess at least the same antioxidant potency as catechins present in green tea, and that the conversion of catechins to TFs during fermentation in making black tea does not alter their free-radical-scavenging activity significantly. Way and coworkers (2004) showed that TF₁, TF₂, and TF₃ significantly inhibited human aromatase activities, the proliferation induced by dehydroepiandrosterone in MCF-7 cells (Figure T.96). In addition, they also had an inhibitory effect on breastcancer cells with hormonal resistance. These findings suggest that black tea TFs may be beneficial in the chemoprevention of hormonedependent breast tumors and represent a possible remedy to overcome hormonal resistance of hormone-independent breast tumors.

TF₂ and TF₃ were found to be slightly more potent in inducing apoptosis in murine myeloid leukemia cells and in reducing both the *in vitro* clonogenicity and *in vivo* tumorigenicity of these cells, representing potential candidates for the treatment of some forms of leukemia (Lung et al., 2004).



Theaflavin (TF1): R₁—R₂=OH

Theaflavin-3-gallate (TF₂A): R₁=Galloyl; R₂=OH

Theaflavin-3'-gallate (TF₂B): R₁=OH; R₂=Galloyl

Theaflavin-3,3'-digallate (TF₃): R₁=R₂=Galloyl

SCHEME T.59 Structure of theaflavins. (From Lambert and Yang, *Mutat. Res.*, 523–524:201–208, 2003. With permission.)

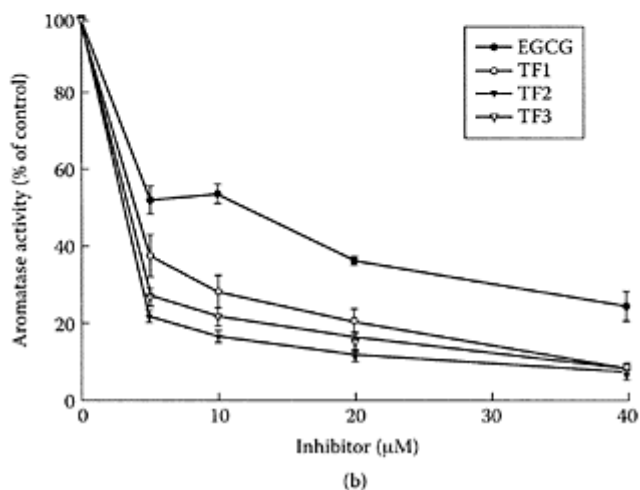
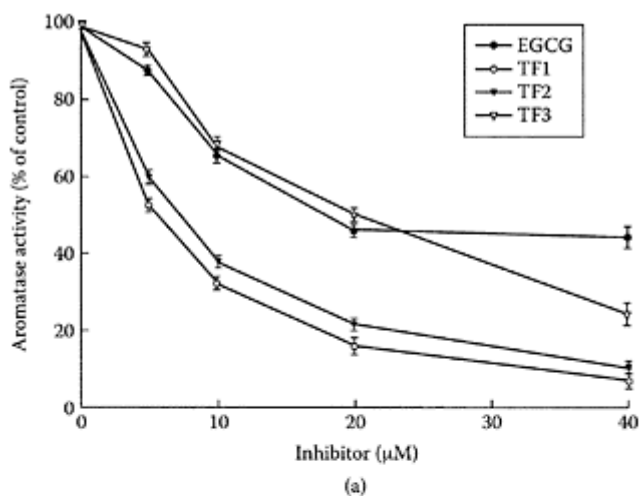


FIGURE T.96 The *in vitro* effects of EGCG and the flavins on aromatase activity from rat ovarian (a) and human placental (b) microsomes. Microsomal-tissue preparations were incubated

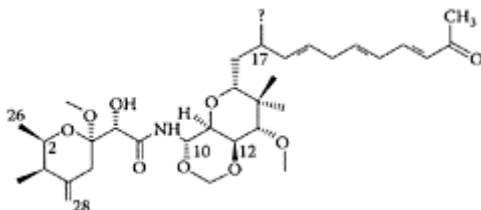
with 0.05 μM [1b-3H] androstenedione and 1 mM nicotinamide adenine dinucleotide phosphate (NADPH) in the presence of EGCG (●), TF-1 (○), TF-2 (▼), or TF-3 (♥) at concentrations ranging from 5 to 40 μM . All measurements were performed in triplicate and represent \pm standard error of the mean (SEM). (From Way et al., *Eur. J. Cancer*, 40:2165–2174, 2004. With permission.)

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Theopederin

Tsukamoto and coworkers (1999) isolated five new bioactive metabolites from the marine sponge *Theonella swinhoei*, theopederins F-J. Of these, theopederin F exhibited antifungal properties against *Saccharomyces cerevisiae* and proved cytotoxic against P388 murine leukemia cells. Later work by Paul



1 $R_1=Me$ $R_2=H$

2 $R_1=H$ $R_2=H$

Theopederins K (1) and L (2). (From Paul et al., *J. Nat. Prod.*, 65:59–61, 2002. With permission.)

et al. (2002) isolated theopederins K and L from the marine sponge *Discodermia* sp., collected from Honduras, with both showing *in vitro* cytotoxicity against P-388 and A-549 cell lines.

The amido trioxadecalin ring system is a common structural motif found in mycalamide, theopederin, and in onnamide families of natural products exhibiting pharmacological activities, including the insect chemical-defense agent pederin and the anticancer and immunosuppressive agents of the mycalamide, theopederin, and onnamide families of natural products (Vuong et al., 2001; Simpson et al., 2000; Rech and Floreancig, 2003).

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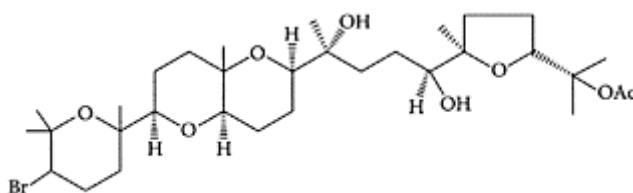
Vuong, D., Capon, R.J., Lacey, E., Gill, J.H., Heiland, K., and Friedel, T., Onnamide F: a new nematocide from a southern Australian marine sponge, *Trachycladus laevispirulifer*, *J. Nat. Prod.*, 64:640–642, 2001.

Thyrsiferyl 23-acetate

Thyrsiferyl 23-acetate (TF23A) is a cytotoxic compound found in marine red alga that specifically inhibits serine/threonine protein phosphatase 2A (Matsuzawa et al., 1994). It induced rapid cell death in various leukemic T- and B-cell lines, which followed a typical apoptotic process (Matsuzawa et al., 1999).

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Thyrsiferyl 23-acetate

(From Matsuzawa et al., *FEBS Lett.*, 356:272–274, 1994. With permission.)

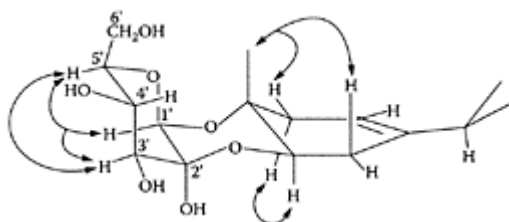
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Thyme

Thyme (*Thymus vulgaris* Labitae) is cultivated in central and southern Europe as a tea, spice, and herbal medicine. The leaf has been used as a stomachic, carminative, diuretic,

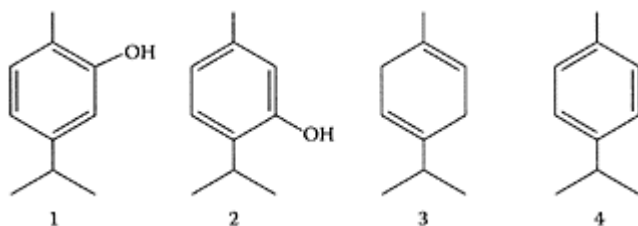
urinary disinfectant, and vermifuge. Tea made from thyme leaf was reported to promote rest and relaxation (Van Den Broucke and Lemli, 1983; Wichtl, 1994). The essential oil in the leaf contains mainly isomeric monoterpene thymol (30–70 percent), carvacrol (3–15 percent), together with other monoterpenoids, such as γ -terpinene and *p*-cymene (Reddy et al., 1998; Rustaiyan et al., 2000; Hudaib et al., 2002) and exhibits strong antimicrobial and antifungal properties (Kalemba and Kunicka, 2003). Kitajima and coworkers (2004) isolated a number of monoterpenes and their glycosides from the polar portion of the methanolic extract of thyme leaf. Based on spectral data, a novel glycoside, thymuside, was identified as *p*-meth-4(5)-ene-1,2-diol and 2-hydroxyhexose, joined by two ether linkages.



Thymuside. (Adapted from Kitajima et al., *Phytochemistry*, 65:3279–3287, 2004.)

Rats maintained on thyme oil or a thyme supplement were found by Youdin and Deans (2002) to have significantly higher antioxidant enzyme activities and total antioxidant status. The proportion of 22:6n-3 in brain phospholipids, which declined with age in control rats, was significantly higher in rats given either supplement. This latter finding is particularly important, as optimum levels of 22:6n-3 are needed for normal brain function.

Thyme has also been used in traditional medicine to treat bronchitis, asthma, and related respiratory diseases. It is well known that nitric



Structures of carvacrol (1) and thymol (2) γ -terpinene (3) and *p*-cymene (4). (Adapted from Burt, *Int. J. Food Microbiol.*, 94:223–253, 2004.)

oxide plays an important role in the pathogenesis of inflammatory diseases. Vigo and coworkers (2004) demonstrated that inhibition of net nitric-oxide production by thyme extract was probably due to its nitric-oxide scavenging activity and its inhibitory effects

on inducible nitric-oxide synthase gene expression. Thymol, isolated from the leaves of thyme, was found to inhibit platelet aggregation induced by collagen, ADP, arachidonic acid, and thrombin (Okazaki et al., 2002).

Thyme oil was reported to inhibit the growth and aflatoxin production by *Aspergillus parasiticus* (Rasooli and Abyaneh, 2004), as well as the growth of *Shigella sonnei* and *Shigella flexneri* (Bagamboula et al., 2004). Aydin and coworkers (2005) recently showed that low concentrations (<0.1 mM) of thyme volatiles, thymols and γ -terpinene, significantly reduced DNA damage in human lymphocytes induced by the heterocyclic amine, 2-amino-3-methylimidazo[4,5-f]-quinoline (IQ) and mitomycin (MMC). Carvacrol, an isomer of thymol, also protected lymphocytes from the genotoxic effects of IQ and MMC, but only at concentrations below 0.05 mM.

An acidic polysaccharide purified from the hot-water extract of thyme leaves was suggested to be a complement activator, which plays an important role in primary-host defense mechanisms (Chun et al., 2001).

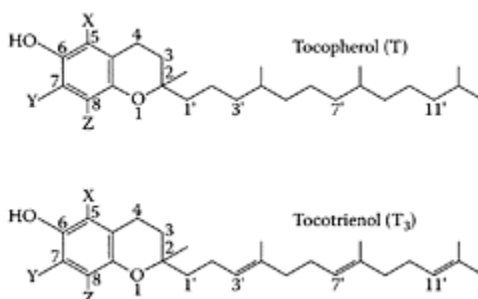
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Tocopherols

see also Vitamin E In nature, vitamin E occurs in eight different forms (α -, β -, γ -, and Δ -tocopherols and α -, β -, γ -, and Δ -tocotrienols) with varying biological activities (Scheme T.60). All forms of vitamin E are present in the diet, e.g., γ -tocopherol in corn and



- (A) α , X=CH₃, Y=CH₃, Z=CH₃
 (B) β , X=CH₃, Y=H, Z=CH₃
 (C) γ , X=H, Y=CH₃, Z=CH₃
 (D) δ , X=H, Y=H, Z=CH₃
 (E) ζ_2 , X=CH₃, Y=CH₃, Z=H
 (F) ϵ , X=H, Y=H, Z=H

SCHEME T.60 Structural formulae of tocopherols and tocotrienols. (From Abidi and Rewnnick, *J. Chromatogr. A*, 913:379–386, 2001. With permission.)

soybean oils, tocotrienols in cereal grains, bran, some nuts, and palm oil.

Epidemiological studies showed an inverse correlation between acute coronary events and high dietary intake of vitamin E (Rimm et al., 1993; Stampfer et al., 1993). Although α -tocopherol is the main vitamin E derivative in the diet, γ -tocopherol in particular has

been shown to have potent antioxidant effects (Wolf, 1997) and was reduced in patients with coronary heart disease (Ohrvall et al., 1996). A preparation of mixed tocopherols rich in γ -tocopherol was found more potent than α -tocopherol alone in decreasing platelet aggregation and intraarterial thrombus formation in rats (Saldeen and Mehta, 1999), processes that play an important role in thrombosis and cardiovascular events.

Halliwell and coworkers (2005) recently argued that tocopherols and tocotrienols may exert direct, beneficial effects in the gastrointestinal tract and that their return to the gastrointestinal tract by the liver through the bile may be physiologically advantageous. These effects are suggested to include binding of prooxidant iron, scavenging of reactive nitrogen, chlorine, and oxygen species, and perhaps inhibition of cyclooxygenases and lipoxygenases.

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Tomato

see also Lycopene Epidemiology studies suggested that a higher intake of tomatoes and tomato products may protect against cardiovascular disease (Arab and Steck, 2000) and reduce the risk of several types of cancer, particularly prostate, lung, and digestive tract (Giovannucci et al., 1999). One of the mechanisms proposed is that tomato extracts inhibit platelet aggregation (Lazarus and Garg, 2004).

The most abundant carotenoid in tomatoes is lycopene (Agarwal and Rao, 2000). It appears to be responsible, in large part, for the potential health benefits of tomato products (Clinton, 1998). Tomatoes showed high antioxidant activities. For example, at

The consumption of tomato products is associated with reduced risk of prostate cancer. Lycopene, the primary red carotenoid in tomatoes, may be the principal phytochemical responsible for this reduction in risk. Lycopene can act as antioxidant, enhance cell-to-cell communication via increasing gap junctions between cells, and modulate cell-cycle progression. Tomatoes also contain folate, vitamin C, significant quantities of potassium, vitamin A, vitamin E, and various other carotenoids and phytochemicals, such as polyphenols, which may also be associated with lower cancer risk (Campbell et al., 2004).

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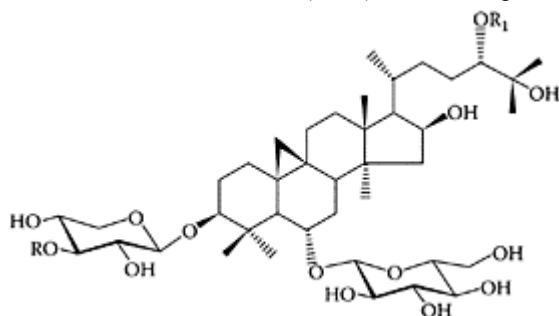
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Triterpene saponins

Triterpene refers to a particular type of molecular structure that has a four- or five-ring, planar-base molecule containing 30 carbon atoms. Triterpene saponins are glycosides, with various sugar molecules attached to the triterpene unit. They have an acidic quality, an acrid-bitter taste, and their function in plants remains unknown. The triterpenes are subdivided into about 20 groups, depending on their particular structures. The base structure is the oleanane triterpene, which may be represented by four forms, oleanolic acid, ursolic acid, and α - and β -amyrin. Platycodin belongs to the very large class of oleanane triterpenes.

Triterpenoid saponins, which are present in plants and some marine animals, exert important pharmacological effects, including cytotoxicity (Haddad et al., 2004), antitumor activity (Setzer and Setzer 2003), antitumor-promoting activity (Yu et al., 2001), anti-inflammatory effects (Smolinski and Pestka 2003), antiallergy and immunomodulatory action (Yesilada et al., 2005), antiviral activity (Chiang et al., 2003), hepatoprotective effects (Kinjo et al., 2003), cardiac activities (Scott et al., 2001), antithrombotic activity (Xu et al., 1997), hypolipemic activity (Lee et al., 2000), central nervous system activity (Liao et al., 2002), and endocrine activity (Chan et al., 2002).

Yesilada and coworkers (2005) found triterpene saponins (Scheme T.61) isolated from



	R	R ₁
1: Brachyoside A	β -D-xylocyr	H
2: Brachyoside C	H	β -D-glucopyr
3: Cyclocanthoside E	H	H

SCHEME T.61 Some triterpene saponins isolated from *Astragalus* species. (From Yesilada et al., *J. Ethnopharmacol.*, 96:71–77, 2005. With permission.)

Turkish *Astragalus* species exhibited prominent IL-2-inducing activity, ranging from 35.9–139.6 percent. This may be the mechanism responsible for its immunomodulatory and anti-cancer effects.

Triterpene saponins obtained from *Albizia adianthifolia* were found to exhibit a cytotoxic effect on human leukemia T cells by induction of apoptosis (Haddad et al., 2004).

Hypoglycemic actions have been reported for the triterpenes of platycodon, bupleurum, polygala, and ginseng (Suttisri et al., 1995). The methanolic extract of the leaves of the Vietnamese plant *Maesa balansae* Mez. (*Myrsinaceae*) was found to possess strong antileishmanial potential, and pentacyclic triterpene saponins were identified as the active constituents (Maes et al., 2004).

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Triticale

Triticale is a hybrid grain that takes its name from the botanical names for wheat (*triticum*) and rye (*secale*). It is known for its higher protein content and it is now grown throughout the United States, primarily in the Midwest. Triticale is found in cereals and in baked goods. It is also available in flake form or as a whole grain or flour. It is a good source of thiamine (0.416 mg), magnesium (130 mg), and folate (73 mg) (in 100 grams).

Recent epidemiological investigations found that whole-grain intake is associated with a reduced risk of chronic diseases, especially cardiovascular disease and diabetes (Jacobs et al., 2004). Three servings of whole-grain foods daily is associated with a reduced risk of coronary heart disease (Jensen et al., 2004). In addition, triticale flours were found to be effective plasma cholesterol-lowering agents (Adam et al., 2001).

Epidemiological studies strongly support the suggestion that high intakes of whole-grain foods protect against the development of type 2 diabetes mellitus (T2DM). People who consume approximately three servings per day of whole-grain foods are also less likely to develop T2DM than low consumers (<3 servings per week) with a risk reduction in the order of 20–30 percent (Venn and Mann 2004).

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Trypsin inhibitor

see also Bowman-Birk protease inhibitor The pancreatic Kunitz inhibitor, also known as aprotinin, bovine basic pancreatic trypsin inhibitor, and trypsin-kallikrein inhibitor, is

one of the most extensively studied globular proteins. Trypsin activity in the pancreas is mainly controlled by the pancreatic secretory trypsin inhibitor, which acts as a potent natural inhibitor of trypsin in order to prevent the occurrence of pancreatitis. When trypsinogen is activated into trypsin in the pancreas, trypsin inhibitor immediately binds to trypsin to prevent further activation of pancreatic enzymes. The inhibitor also blocks the further activation of pancreatic cells via the trypsin receptor (Hirota et al., 2003).

Pancreatic trypsin inhibitor has a relatively broad specificity, inhibiting trypsin-like, as well as chymotrypsin-like and elastase-like, serine (pro)enzymes endowed with very different primary specificity. It reacts rapidly with serine proteases to form stable complexes. This inhibitor, the Bowman-Birk trypsin inhibitor (BPTI) inhibits the nitric-oxide synthase type I and type II action and impairs K⁺ transport by Ca²⁺-activated K⁺ channels. Clinically, the use of BPTI in selected surgical interventions, such as cardiopulmonary surgery and orthotopic liver transplantation, is advised, as it significantly reduces hemorrhagic complications and thus blood-transfusion requirements (Ascenzi et al., 2003).

Tumor-associated trypsin inhibitor was initially isolated from the urine of a patient with ovarian cancer. It is a peptide produced at high concentrations by several tumors. It is identical to pancreatic secretory trypsin inhibitor. It is a prognostic marker for ovarian, bladder, and kidney cancer, which may be associated with the participation of trypsin in protease cascades contributing to tumor invasiveness (Stenman, 2002.)

Trypsin inhibitors are widely distributed in plant seeds; the most examined plant inhibitors are found in the species of the families *Leguminosae*, *Graminae*, and *Solanaceae*. Feeding experiments on diets containing isolated soybean trypsin caused insignificant growth depression in rats and chicks, but induced enlargement of the pancreas in rats, chicks, and mice but not in pigs, dogs, calves, monkeys, and presumably humans (Birk, 1996). Findings on the involvement of trypsin inhibitor (Kunitz) and of the Bowman-Birk trypsin inhibitor (BBTI), which possesses two independent sites of inhibition, one against trypsin and the other against chymotrypsin (Birk, 1985), in prevention of tumorigenesis suggest a possible positive contribution of the inhibitors. BBTI is also an effective inhibitor of nephrotoxicity induced by the antibiotic gentamicin. It does not cause side effects and does affect the antimicrobial activity (Birk, 1996). Recently, it has been reported that a trypsin inhibitor from *Peltophorum dubium* seeds caused apoptosis of concanavalin A-stimulated mouse lymphocytes, whereas it had no effect on normal mouse splenocytes or lymphocytes (Fernanda et al., 2003). The *in vitro* effects of these inhibitors on animals should be interpreted with caution when related to humans. Trypsin inhibitor from the seeds of *Clausena lansium* reduced the activity of HIV-1 reverse transcriptase and exerted anti-fungal activity toward *Physalospora piricola* (Ng et al., 2003).

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Turmeric

see also Curcumin Turmeric is a spice that comes from the root *Curcuma longa*, a member of the ginger family, *Zingiberaceae*. In Indian traditional medicine, turmeric has been used for its medicinal properties for treating various ailments, such as biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism, and sinusitis (Ammon et al., 1992) and through different routes of administration, including topically, orally, and by inhalation.

Clinical studies demonstrated that administration of turmeric powder to different patients with respiratory diseases relieves symptoms like dyspnea, cough, and sputum or physical signs. Treatment of patients with rheumatoid arthritis also showed a real improvement (Ammon and Wahl, 1991). Turmeric can lower lipid peroxidation by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase at higher levels (Pulla Reddy & Lokesh, 1992).

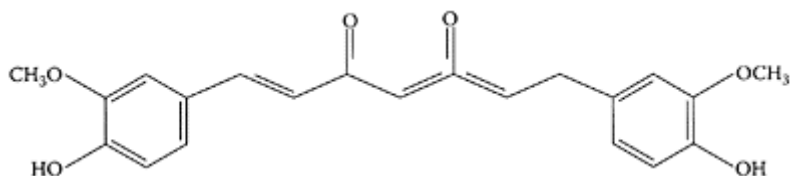
Curcuminoids are major components of turmeric, which include mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin. A large number of studies on the antioxidant (Unnikrishnan and Rao 1999), anti-inflammatory (Chainani-Wu, 2003), antiviral (Mazumder et al., 1995), anticancer (Aggarwal et al., 2003), and antifungal properties of curcuminoids were identified. Curcumin has been shown to be safe in six human trials and has demonstrated anti-inflammatory activity by inhibition of a number of different molecules, such as phospholipase, lipoxygenase, cyclooxygenase 2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12, that play a role in inflammation (Chainani-Wu, 2003). In addition, the wound-healing and detoxifying properties of curcumin have also received considerable attention (Joe et al., 2004).

Recently, curcumin was shown to have radio-sensitizing effects on squamous carcinoma cells by arresting at the S/G2M phases of the cell cycle (Khafif et al., 2005). Treatment with curcumin prior to radiation significantly decreased the ability of cancerous cells to colonize compared to the control (without added curcumin). These results were consistent with earlier studies in which curcumin induced apoptosis and cell

death in colon carcinoma cells and human cancer-cell lines (Jiang et al., 1996; Chen et al., 1999).

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Turmeric curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]. (From May et al., *Anal. Biochem.*, 337:62–69, 2005. With permission.)

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Tyrosinase inhibitor

Tyrosinase is known to be a key enzyme in melanin biosynthesis, involved in determining the color of mammalian skin and hair. Various dermatological disorders, such as melasma, age spots, and sites of actinic damage, arise from the accumulation of an excessive level of epidermal pigmentation. Tyrosinase inhibitors have become increasingly important in medication and in cosmetics to prevent hyperpigmentation by inhibiting enzymatic oxidation.

A number of naturally occurring tyrosinase inhibitors have been described (Curto et al., 1999; Matsuda et al., 1996; Kubo and KinstHori, 1999; Kim et al., 2005). Many are polyphenol derivatives of flavonoids or of trans-stilbene (t-stilbene), such as resveratrol and its derivatives, which have been investigated intensively. They are usually constructed from one of two distinct substructures, which dictate their mechanism of tyrosinase inhibition: containing either a 4-substituted resorcinol moiety or catechol. The 4-substituted resorcinol group has been reported to be a potent tyrosinase inhibitor (Shimizu et al., 2000).

Another group of compounds, with a similar structure to t-stilbene, is the chalcones, which are widely distributed in higher plants and were recently demonstrated as potential inhibitors of tyrosinase (Nerya et al., 2003, 2004). Other potentially active agents, such as kojic acid (5-hydroxy-4-pyran-4-one-2-methyl), a fungal metabolic product, and arbutin (hydroquinonebeta-D-glucopyranoside), a glycosylated hydroquinone found at high concentrations in certain plants, have not yet been demonstrated as clinically efficient (Nakagawa and Kawai, 1995). Hydroquinone, a widely used skin-lightening agent, is a compound considered to be cytotoxic to melanocytes and, hence, potentially mitogenic (Frenk, 1995; Dooley, 1997; Hermanns et al., 2000). As a result of these and other side effects, there has been increasing impetus to find alternative herbal depigmenting agents.

Azelaic acid is a naturally occurring, saturated dicarboxylic-acid originally isolated from *Pityrosporum ovale* and is a rather weak competitive inhibitor of tyrosinase *in vitro*. In addition, azelaic acid has a cytotoxic effect on melanocytes (Schallreuter and Wood, 1990). Several other natural compounds (Seo et al., 1999; Shin et al., 1998), such as quercetin, myricetin, and glycoside of myricetin, have been reported to have various degrees of inhibitory activity toward tyrosinase (Matsuda et al., 1996), and flavonoids and stilbenes obtained from *Artocarpus incisus* and other plants also suggest that compounds having the 4-substituted resorcinol skeleton have potent tyrosinase inhibitory ability (Shimizu et al., 2000). However, the effective topical concentration of these compounds in disorders of hyperpigmentation is not yet known. Among the licorice constituents, glabridin exhibited superior activity compared to that of glabren, isoflavene, and ILC, a chalcone (Nerya et al., 2003).

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U

Uncaria tomentosa

see also Cat's claw, Quinic acid Hot-water extracts from the vine *Uncaria tomentosa* were reported to affect immune function (Aquino et al., 1991; Lemaire et al., 1999). Such effects were later shown to include inhibition of TNF α (Sandoval et al., 2000) and activation of the central transcription nuclear factor κ B (NF- κ B) (Sandoval-Chacon et al., 2002; Akesson et al., 2003). A hot-water extract from the bark of *Uncaria tomentosa*, C-Med 100[®], in which large molecules, such as tannins and flavonoids, had been removed, still enhanced DNA repair (Sheng et al., 2000) and protected against "spontaneous" apoptosis induction *in vitro* (Akesson et al., 2003). It also inhibited proliferation of tumor cells without inducing apoptosis or necrotic cell death. Subsequent work by Akesson et al. (2005) identified quinic acid as one of the components responsible for these effects.

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Uva ursi

see also Bearberry Uva ursi is a compound extracted from the bearberry plant (*Arctostaphylos uva ursi* L.). This herb is used for treating lower urinary-tract infections and is currently recommended for the treatment and prophylaxis of cystitis (Larsson et al., 1993; Yarnell, 2002). Uva ursi, however, causes depigmentation by inhibiting tyrosinase kinase and hence melanin synthesis (Matsuda et al., 1996). Wang and Del Priore (2004) recently reported a case of bilateral bull's eye maculopathy in a patient ingesting tea made from uva ursi over a three-year period to treat a recurrent urinary-tract infection. Based on these results, they cautioned against the use of uva ursi, which should be considered a retinal toxic drug.

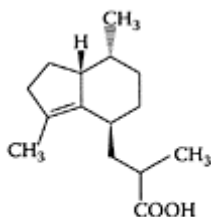
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V

Valerenic acid

see also Valerian Valerenic acid, a hydrophilic sesquiterpenoid, and its derivatives are the major active constituents in the herb valerian (*Valeriana officinalis*). Valerian, an herbal medicine, is used primarily for its sleep-enhancing and sedative effects (McCabe, 2002). Gao and Bjork (2000) found valerenic-acid derivatives varied from 11.65–0.15 mg/g in different varieties of Valeriana.



Valerenic acid

Adapted from Fernandez, S., et al., *Pharmacol. Biochem. Behav.*, 77:399–404, 2004.

Micropropagation proved to be a much more reliable and effective method for optimizing the bioactive constituents in *V. officinalis* compared to seed-propagated plants. Valerenic acid was shown by Reidel et al. (1982) to inhibit the enzyme system, causing GABA breakdown in the brain. The resulting increase in GABA is associated with sedation and decrease in CNS activity.

References

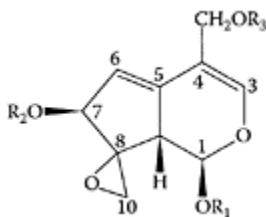
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Valepotriates

see also Valerian Valepotriates, naturally occurring iridoids or cyclopentan-c-pyran monoterpenoids, are found in many plants, including the herb valerian. Together with valerenic-acid derivatives, they are considered to be the active constituents of valerian (Gao and Bjork, 2000). Unlike the hydrophilic valerenic-acid derivatives, valepotriates are hydrophobic and can be divided into four main groups based on their chemical structure. These include diene, monoene, valtrate-hydrine, and desoxy monoene types. The diene types are shown in Scheme V.62 (Bos et al., 2002). Valepotriates, mainly present in the roots, are thought to dampen the central-nervous system by exhibiting activity between sedation and tranquilization and are referred to aequilans (Von Eickstedt and Rahman, 1969). Bos et al. (2002) reviewed the properties of valepotriates, as well as the qualitative and quantitative methods used for their analysis.

References

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	R ₁	R ₂	R ₃	
1	Iv	Iv	Ac	Valtrate
2	Iv	Ac	Iv	Isovaltrate
3	Aiv	Iv	Ac	Acevaltrate
4	Iv	Ac	Ac	Diavaltrate
5	Iv	Aiv	Ac	Homoacevaltrate
6	Miv	Iv	Ac	1-Homovaltrate
7	Iv	Ac	Miv	7-Homovaltrate

8	Iv	Ac	Aiv	11-Acevaltrate
9	Iv	Hiv	Ac	Hydroxyvaltrate
10	Cr	Iv	Ac	1-Seneciovaltrate (isohomoacevaltrate)
11	Iv	H	Iv	Deacetylisovaltrate

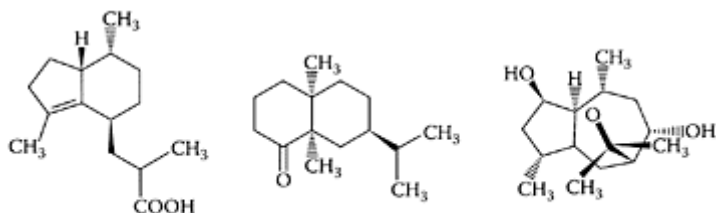
SCHEME V.62 *Valepotriates* (diene type). (From Bos et al., *J.Chromatogr.*, A 967:131–146, 2002. With permission.)

Valerian

see also Valerenic acid and Valepotriates Valerian (*Valeriana officinalis*), an herbal medicine, is used primarily as a tranquilizer and sleep inducer (Reynolds, 1996). The effects of valerian are attributed to a number of different compounds present as volatile-oil components. These include monoterpenes, although it is the biological activity of the sesquiterpene components that have received the most attention. The latter includes valerenic acid, valeranone, and kessyl glycol.

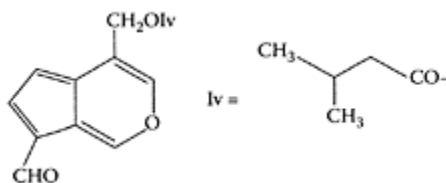
Valerenic acid and kessyl-ring systems are unique to valerian. Valerenic acid appears to inhibit the enzymatic degradation of GABA in the brain (Reidel et al., 1982). This results in increased GABA levels that are associated with sedation and CNS activity (Houghton, 1999). In contrast, valeranone acts primarily on the muscle rather than on the CNS (Hazelhoff et al., 1982).

A novel group of irioid-like monoterpenes, the valepotriates, were also identified in *Valeriana* (Mannerstatter et al., 1966; Thies, 1966). These were esters with moderate polarity, requiring extraction with alcoholic solvents. The tranquilizing effects of valepotriates, as measured by a decrease in spontaneous motility in mice, was clearly shown by Von Eikstedt (1969) and Von Eikstedt and Rahman (1969). The major degradation product of valepotriates by the intestinal bacteria flora was homobaldrinal and related products. Homobaldrinal was found by Wagner et al. (1980) to have a greater effect on spontaneous motility in mice compared to the parent valepotriates, suggesting valepotriates may act as prodrugs.



Valerenic acid, Valeranone, Kessyl glycol

Adapted from Fernandez et al., *Pharmacol. Biochem. Behav.*, 77:399–404, 2004, and Tori et al., *Phytochemistry*, 41:977–979, 1996.



Homobaldrinal. (From Hui-lian et al., *Toxicol. Appl. Pharmacol.*, 188:36–41, 2003. With permission.

There is considerable controversy, however, over the efficacy of valerian in the treatment of insomnia. A systematic review of the effect of valerian on insomnia in nine randomized clinical trials by Stevinson and Ernst (2000) showed great discrepancies among trials. Some studies showed promising but inconclusive results, while others found valerian had no acute and cumulative effects on sleep. Using a series of randomized trials, Coxeter and coworkers (2003) found no improvement of valerian over the placebo in reducing chronic insomnia symptoms in patients. A recent study on healthy volunteers by Gutierrez et al. (2004) found acute administration of valerian had no mood-altering or psychomotor/cognitive effects. Poyares and coworkers (2002), however, reported valerian had a beneficial effect on improving the sleep of insomniacs after benzodiazepine withdrawal. Problems associated with the long-term use of this drug are dependency, tolerance, long-term memory, and altered sleep structure. Low doses of dichloromethane extracts of valerian were not found by Hui-lian et al. (2003) to have any significant cytotoxicity or genotoxicity on human endothelial ECV304 cells, but did cause moderate DNA damage at higher doses as a result of oxidative stress. Both vitamins E and C attenuated the effect of high doses of the valerian extract, suggesting definite guidelines are needed for clinical therapy with valerian.

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Vegetable oils

see Canola, Corn, Flax, Soybean, and Sunflower oils

Vegetables

see also Individual vegetables The presence of bioactive phytochemicals, in addition to vitamins and provitamins, in vegetables and fruits is associated with a decreased risk of cancer (Block et al., 1992; Steinmetz and Potter, 1991) and cardiovascular disease (Grey et al., 1993; Gramenzi et al., 1990; Hertog et al., 1993). Broekmans and coworkers (2000) showed that the consumption of fruits and vegetables by 47 male and female volunteers significantly increased plasma carotenoids and vitamins, while decreasing homocysteine. The latter has become a useful biomarker, as epidemiological studies have shown an inverse relationship between plasma homocysteine and cardiovascular disease. Chu and coworkers (2002) examined 10 common vegetables based on their consumption per capita data in the United States. Broccoli contained the highest levels of total phenols (101.6 mg/g), followed by spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, celery, and cucumber. Using the Total Oxygen Scavenging (TOSC) assay, red pepper had the highest antioxidant activity (46.95 mmol of vitamin C equiv/g of sample), followed by broccoli, carrot, spinach, cabbage, yellow onion, celery, potato, lettuce, and cucumber. These researchers also proposed a phenolic-antioxidant index (PAI) for evaluating the quantity/quality of phenolic s in these vegetables by eliminating vitamin C's antioxidant contributions. Using HepG₂ liver-cancer cells, spinach was found to have the highest antiproliferative activity, followed by cabbage, red pepper, onion, and broccoli. Based on these results, a bioactivity index (BI) for cancer prevention was proposed to help consumers select vegetables on the basis of their health benefits. For example, because red pepper and spinach had the highest antioxidant and antiproliferative activities, they were used as controls to calculate BI.

A recent study by Ismail et al. (2004) was unable to find any relationship between antioxidant activity and total phenolics for commonly selected vegetables in Malaysia. Spinach was very high in total phenols, followed by swamp cabbage, kale, shallots, and cabbage. A 1-min thermal treatment, involving boiling 300 g of each vegetable in 500 mL water, significantly ($p < 0.05$) decreased the total phenolic content in all the vegetables examined.

Rijken et al. (1999), using aberrant crypt multiplicity as the marker for colorectal cancer, found that vegetable consumption (freeze-dried peas, spinach, sprouts, and broccoli) had a beneficial effect on colorectal cancer by inhibiting early postinitiation events, but were more pronounced in the advanced lesions. These researchers, however, found that α - and β -carotenoids made only a marginal contribution to the observed beneficial effects.

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Vinegar

see also Kurosu As an acidic seasoning, vinegar is reported to have medicinal properties due to its physiological functions, such as digestive, appetite-stimulating, and exhaustion-recovering effects. One of the most common traditional Japanese vinegars obtained from unpolished rice is kurosu. In addition to preventing hypertension by improving blood fluidity, Nishidai et al. (2000) showed an ethylacetate extract of kurosu exhibited antitumor properties arising, in part, from its suppression of lipid peroxidation.

Vinegar is also a by-product of Sherry wines by a dynamic aging process known as “*solaras and criaderas*” Recent work by Alonso et al. (2004) demonstrated the antioxidant power of vinegar, which was highly influenced by its polyphenolic content (Figure V.97). Correlation analysis was obtained for compounds identified in more than two samples. Gallic acid was particularly important in vinegar without aging, while cis-p-coumaric acid, 1-ferulic and syringic acids, together with vanillin and p-hydroxybenzaldehyde, exhibited high correlations for vinegars aged in wood.

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Vitamins

see also Individual vitamins, as well as Niacin and Folate Oxidative stress is the major contributor to many degenerative or chronic diseases, such as coronary heart disease, cancers, and neurodegenerative diseases. These result from the biological damage to lipids, proteins, and nucleic acids brought about by the production of reactive-oxygen species. To protect the body from the deleterious effects of reactive-oxygen species, endogenous antioxidants are present, including antioxidant vitamins. A review by McCall and Frei (1999), however, pointed out that studies on smokers and non-smokers revealed that only vitamin A, and possibly vitamin C, could reduce lipid-oxidative damage. Kriharides and Stocker (2002), in reviewing the data from a number of major, randomized studies, were unable to find any evidence for recommending α -tocopherol or β -carotene supplements in treating coronary heart disease.

A review of a number of randomized trials by Mitchell et al. (2003) found that supplementation with vitamins and minerals enhanced immune function of the elderly. The primary

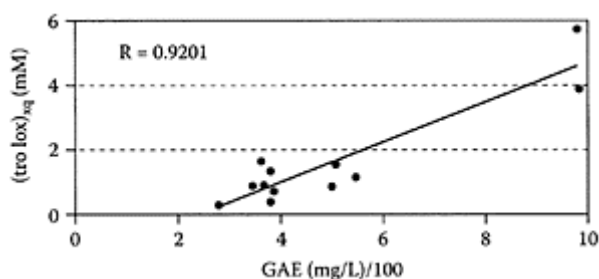


FIGURE V.97 Correlation line between total polyphenolic index (GAE) and antioxidant power ([Trolox]_{eq}) of vinegars. (From Alonso et al., *Food Res. Int.*, 37:715–722, 2004. With permission.)

vitamins involved were vitamins E, C, A, and β -carotene. In a double-blind, placebo-controlled trial with 1078 Tanzanian women infected with HIV, Fawzi et al. (2004) showed that a daily multivitamin supplement of vitamins (vitamins A [preformed and β -carotene], B, C, and E), slowed down the progression of HIV. The supplement significantly reduced fatigue, rash, and upper-respiratory infections and provided a low-cost strategy for delaying implementation of antiretroviral therapy.

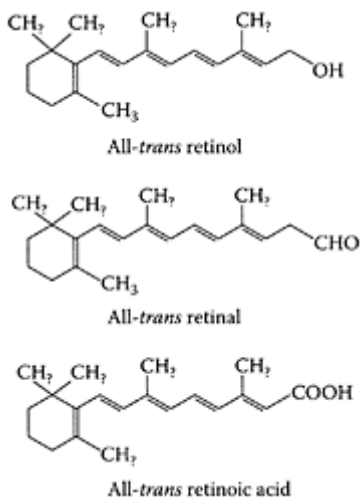
The evidence for the protective nature of vitamin supplements in humans is mixed and still requires further studies.

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Vitamin A

see also **β -Carotene, Retinoic acid, and Retinol** Vitamin A was one of the first vitamins discovered, but many of its functions are still poorly defined. The physiological active forms of vitamin A are retinol, retinal, and retinoic acid (Scheme V.63). The hydrophobic polyene chain in vitamin A is responsible for its ability to quench singlet oxygen, neutralize thiyl radicals, and combine and stabilize peroxy radicals (Palace et al., 1999). These researchers reported that while epidemiological and experimental studies support the possible benefits of vitamin A in reducing heart disease, several large, intervention studies did not. Further confusion was provided by the fact that β -carotene supplementation can actually increase cardiovascular and cancer-related mortality.



SCHEME V.63 Structure of all-*trans*-retinol, all-*trans*-retinal, and all-*trans*-

retinoic acid. (From Ono et al., *Exp. Neurol.*, 189:380–392, 2004. With permission.)

Talas et al. (2003), however, demonstrated the benefits of vitamin A therapy in healing tracheal anastomoses in adult Wistar rats by reversing the deleterious effects of the corticosteroid dexamethasone. A recent study by Ono et al. (2004) speculated that vitamin A and β -carotene could prevent the development of Alzheimer's disease. This disease is characterized by the deposition of amyloid β -peptide (Ab) as amyloid plaques and vascular amyloid and neurofibrillary tangles (Selkoe, 2001). *In vitro* studies by Ono et al. (2004) showed that vitamin A and β -carotene inhibited the formation of β -amyloid fibrils (fAb) from fresh amyloid β -peptide (Ab), as well as their extension. In addition, vitamin A and β -carotene destabilized preformed f Ab in a dose-dependent manner. The relative potency of their antiamyloidogenic and fibril-destabilizing effects ranged from highest for retinol and retinal, followed by β -carotene, and then retinoic acid. These results pointed to the application of these molecules in the prevention and therapy of Alzheimer's disease.

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Vitamin B₃

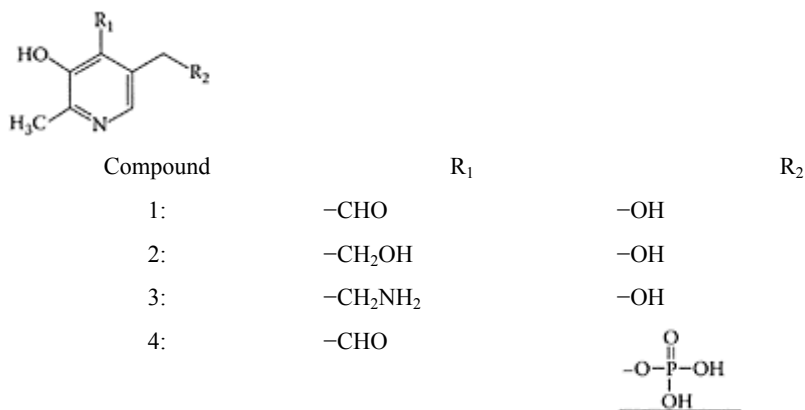
see Niacin

Vitamin B₆

The different natural forms of vitamin B₆, pyridoxine, pyridoxal, and pyridoxamine, are all converted *in vivo* to the active coenzyme form, pyridoxal-5'-phosphate (Scheme

V.64). Pyridoxal-5'-phosphate is involved in a wide range of synthetic and catabolic processes, as well as the interconversion of amino acids, biosynthesis of carbohydrates, proteins, lipids, and nucleic acids (Brody, 1999). In addition, pyridoxal-5'-phosphatedependent enzymes are also involved in the synthesis of such neurotransmitters as GABA, norepinephrine, dopamine, serotonin, and poly amines. The possible role of B₆ in normal neuronal development became evident when vitamin B₆ was deficient (Kirskey et al., 1990). Geng and coworkers (1997) reported pyridoxal phosphate protected cultured hippocampal neurons from glucose deprivation-induced damage. Wang et al. (2002) found vitamin B₆ protected monkey retinal neurons from ischemic damage, with the potential as a novel pharmacotherapy.

Previous studies on the suppression of animal and human cancer cells *in vitro* by high levels of vitamin B₆ pointed to its ability to act as a chemopreventive agent (DiSorbo and Litwack, 1983; Di Sorbo et al., 1985; DiSorbo and Nathanson, 1983; Molina et al., 1997). The anticancer properties of vitamin B₆ against colon cancer were first reported in case-control studies in the United States by Slaterry et al. (1997). They found an inverse association



SCHEME V.64 Chemical structures of vitamin B₆ compounds. Compound 1, pyridoxal (PL); compound 2, pyridoxine (PN); compound 3, pyridoxamine (PM); and compound 4, pyridoxal 5'-phosphate (PLP). (Mizushina et al., *Biochem. Biophys. Res. Commun.*, 312:1025–1032, 2003. With permission.)

between the risk for colon cancer and vitamin B₆ intake. Confirmation of the protective role of vitamin B₆ against colorectal cancer was provided by Jansen et al. (1999) based on case-control studies conducted in seven European countries. An inverse relationship was also reported between vitamin B₆ and the risk for prostate and lung cancers (Hartman et al., 2001; Key et al., 1997). Moderate doses of vitamin B₆ were also reported by Komatsu

et al. (2001) to significantly suppress the development of colonic tumors in azoxymethane (AOM)treated mice. The anticancer effect of vitamin B₆ was shown by Matsubara et al. (2001) to be due, in part, to inhibition of angiogenesis. Further elucidation of the antiangiogenesis and anticancer mechanisms of vitamin B₆ by Mizushina et al. (2003) showed pyridoxal-5'-phosphate-inhibited, replicative DNA polymerases and human cancer-cell proliferation.

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Vitamin B₁₂

Vitamin B₁₂, or cobalamin, is a complex molecule containing a cobalt-centered, corrin nucleus. It functions as a coenzyme by resynthesizing methionine from homocysteine with 5-methyl tetrahydrofolic acid as the methyl-group donor (Marsh, 1999). In addition, it provides tetrahydrofolic acid for other folate-dependent reactions (Selhub, 2002). Animal organ meats, such as liver and kidney, are particularly rich sources of cobalamin, although it is synthesized exclusively by bacteria (Herbert, 1996; Raux et al., 2000). Because the synthesis of cobalamin by intestinal bacteria is insufficient, dietary sources of vitamin B₁₂ must be provided in the diet (Herbert, 1988).

Traditionally, vitamin B₁₂ deficiency has been associated with pernicious anemia, a condition characterized by poorly formed, large red blood cells and demyelination of sheaths of nerve cells (Gropper, 2000). Current research associates deficiency of vitamin B₁₂ with increased risk for atherosclerosis (Nygard et al., 1999; Brattstrom and Wilcken, and Jackson, 2000; Mangoni et al., 2002) and neurodegenerative diseases (Selhub et al., 2000; Rosenberg et al., 2001). Wolters et al. (2004) pointed out that vitamin B₁₂ deficiency is particularly prevalent among the elderly population and recommends supplementation of >50 mg/day.

A review of Alzheimer' disease by Luchsinger and Mayeux (2004) reported that some studies suggest that a high intake of vitamins, including B₁₂, lowered the risk for this disease. However, based on a number of different studies, no definite conclusions or recommendations could be made. This was borne out in a recent study by Mizrachi et al. (2004), who found no significant association between plasma total homocysteine, B₁₂, and folate levels in either healthy or Alzheimer's patients in Israel.

An abnormal vitamin B₁₂ status was reported in depressed patients by Bell et al. (1991), while epidemiological data from a Women's Health and Aging Study suggested a twofold risk of severe depression was associated with a deficiency of this vitamin (Pennix et al., 2000). However, a recent three-month, randomized, placebo-controlled study of 140 individuals deficient in vitamin B₁₂, assessed by an increase in plasma methyl-malonic acid, found no improvement in cognitive function or symptoms of depression following supplementation with the vitamin.

Even though few studies evaluated visualevoked potential (VEP) changes after vitamin B₁₂ supplementation, Pandey and coworkers (2004) showed that visual pathways were vulnerable to vitamin B₁₂ deficiency. The prolonged VEP associated with patients suffering from vitamin B₁₂ deficiency was found to return to normal following vitamin B₁₂ supplementation.

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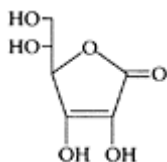
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Vitamin C

see also Ascorbic acid Vitamin C, or L-ascorbic acid, is a water-soluble anti-oxidant widely distributed in fruits and vegetables. AM et al. (2003) showed vitamin C protected LDL from homocysteine-mediated oxidation via dehydroascorbic acid. Homocysteine, an atherogenic amino acid, appears to promote iron-dependent oxidation of LDL. Thus, vitamin C may have a role in the prevention of cardiovascular disease. Guaiquil et al. (2003) confirmed the prominent cardioprotective effect of vitamin C in ischemic myocardium. Rat cardiomyocytes accumulated vitamin C by transporting only dehydroascorbic acid (DHA), the oxidized form of vitamin C. Thus, treatment with DHA inhibited hypoxia-induced damage and decreased apoptosis by preventing expression of

Bax, caspase-3 activation, and cytochrome C translocation into the cytoplasm. These results pointed to the potential therapeutic value of DHA. A recent study by Wu et al. (2004) showed that the microvascular benefits



of vitamin C in septic patients may be due to its inhibition of inducible nitric-oxide synthetase (iNOS).

Epidemiological studies pointed to the protective role of antioxidants in fruits and vegetables against cancer (Michels et al., 2000; Vecchia et al., 2001). Of the major antioxidants in fruits and vegetables, vitamin C was reported to prevent oxidative-stress-mediated chronic diseases, including cancer, cardiovascular disease, hypertension, stroke, and neurodegenerative diseases. The U.S. Department of Agriculture and National Cancer Institute recommend a minimum consumption of five servings of fruits and vegetables per day to prevent cancer. Based on this recommendation, 200–280 mg of vitamin C would be consumed. However, conflicting results have been obtained regarding the beneficial effects of vitamin C in cancer prevention. *In vitro* studies by Lee et al. (2001) showed vitamin C-induced decomposition of lipid hydroperoxides to endogenous genotoxins capable of causing DNA damage. These results suggested that the amount needed in the diet was equivalent to a daily consumption of 200 mg of vitamin C. However, the amount of lipid peroxides used in the study was 400 mmol/L, which far exceeded the levels normally found in human blood, which ranged from 10–500 nmol/L (Zamburlini et al., 1995). In addition, endogenous antioxidants, such as glutathione peroxidase and catalase, are also present. Nevertheless, questions have been raised regarding the effectiveness of vitamin C in cancer prevention. Lee et al. (2003) reappraised the role of vitamin C in cancer prevention, suggesting that it is the flavonoid components in fruits and vegetables that are primarily responsible for the observed chemopreventive effects.

Wenzel and coworkers (2004) showed that as an antioxidant, ascorbic acid interfered with drug-induced (camptothecin or flavonoid flavone) apoptosis of HT-29 human colon-carcinoma cells. By dramatically reducing the production of reactive-oxygen species in the mitochondria, ascorbic acid blocked apoptosis of the cancer cells by inhibiting disintegration of the plasma membrane (Figure V.98). In addition,

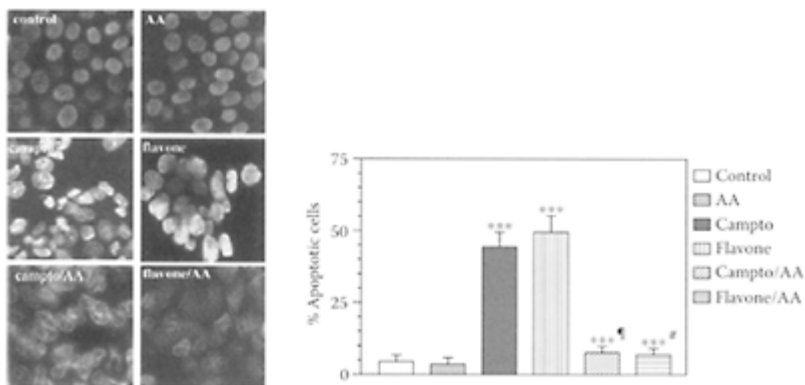


FIGURE V.98 Camptothecin-mediated and flavone-mediated plasma-membrane disintegration is reduced by ascorbic acid. Membrane disintegration in cell treated with medium alone (control), or with 1 mM ascorbic acid, or with 50 mM camptothecin (campto), or 150 mM flavone in the absence or presence of 1 mM ascorbic acid (AA) was assessed by uptake of Hoechst 33342 after 24 h. The percentage of apoptotic cells at 24 h is given in the lower panel. *** $p < 0.001$ versus control cells or versus cells treated with and camptothecin or # flavone. (From Wenzel et al., *Carcinogenesis*, 25:703–712, 2004. With permission.)

ascorbic acid prevented caspase-3 stimulation, downregulation of the mitochondrial antiapoptotic protein bcl-X_L, and NF- κ B mRNA levels. Thus, there may be a need to reduce ascorbic acid intake in patients undergoing a course of chemotherapy for tumors.

Verrax and coworkers (2003) reported that a combination of vitamins C and K₃ effectively killed cancer cells by a new type of cancer-cell death known as autophagy. This process was caspase-3-independent and characterized by oxidative stress, DNA fragmentation, and cell membrane damage, with progressive loss of organelle-free cytoplasm. These researchers proposed vitamins C and K₃ be considered adjuvants for cancer therapy. Park and coworkers (2004) reported that L-ascorbic acid induced apoptosis in acute myeloid-leukemia cells. The daily administration of up to 100 g of L-

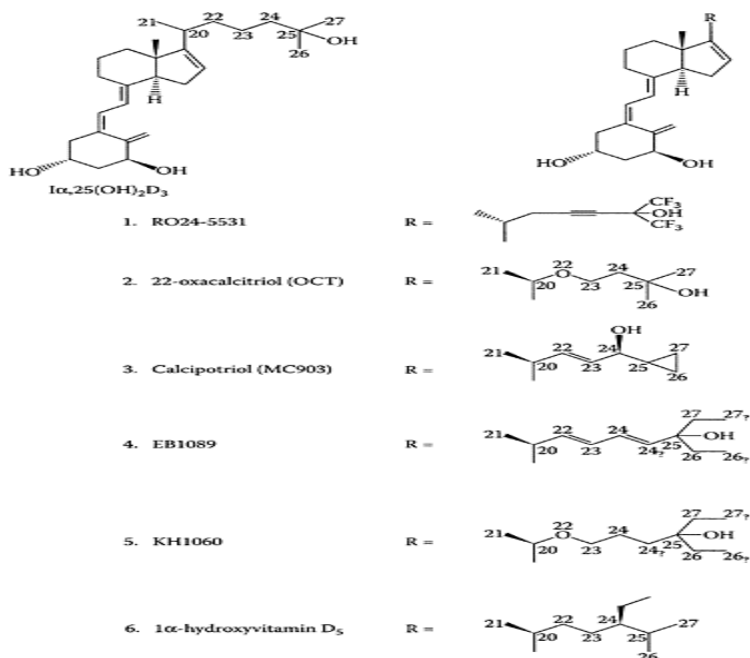
ascorbic acid proved beneficial to patients with acute myeloid leukemia. The mechanism appeared to involve the production of H_2O_2 from the oxidation of reduced glutathione by L-ascorbic acid.

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Vitamin D

Vitamin D consists of a family of 9,10 secosteroids differing in their side-chain structure (Mehta and Mehta, 2002). The main one, vitamin D₃, in its biological form, is inactive but metabolizes into the active form, 1- α -25-dihydroxy D₃, which plays a crucial role in calcium and bone homeostasis. The active form has been shown to prevent the growth of many neoplastic cells in prostate cancer (Lokeshwar et al., 1999), breast cancer (Pirianov and Colston, 2001), osteosarcoma (Hansen et al., 2001), and colon carcinoma (Diaz et al., 2000), but its use in cancer prevention is limited by its calcemic activity. The levels needed to suppress the growth of neoplastic cells would cause hypercalcemia and death (Mehta et al., 1997). To overcome this problem, a number of vitamin D₃ analogues were developed to reduce calcemic activity without compromising its antiproliferative activity. The vitamin D structure consists of four parts, including A, B, C, and D rings, plus the side chain. Most of the analogs involved modification in the A and B rings, such as calcipotriol, 2,2-oxacal-citrol, KH 1060, 1- α -25 (OH)₂D₃, and EB 1089, as shown in Scheme V.65.



SCHEME V.65 Chemical structure of some active analogs of vitamin D.
(From Mehta and Mehta, *J. Nutr.*

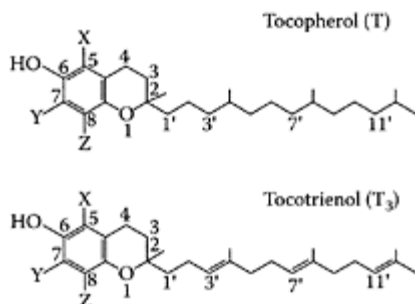
Biochem., 13:252–264, 2002. With permission.)

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Vitamin E

see also Tocopherols Vitamin E is a mixture of fat-soluble vitamins classified as tocopherols or tocotrienols. Tocopherols have a 16-carbon isoprenoid side chain, while tocotrienols have three, unsaturated double bonds in the 16-carbon isoprenoid side chain. Four different isomers are recognized, based on the number and position of the methyl groups in the ring structure, and are designated α , β , γ , and δ (Scheme V.66). While tocopherols are widely distributed in foods, tocotrienols are found in only a limited number of foods, such as palm oil. The major tocopherol in mammalian foods is α -tocopherol, followed by γ -tocopherol. They both act as chain-breaking antioxidants by the phenoxyl group, interacting with scavenging free radicals. There is strong epidemiological evidence between elevated tocopherol levels in the blood and protection against



- (A) α , X=CH₃, Y=CH₃, Z=CH₃
 (B) β , X=CH₃, Y=H, Z=CH₃
 (C) γ , X=H, Y=CH₃, Z=CH₃
 (D) δ , X=H, Y=H, Z=CH₃

SCHEME V.66 Structural formulae of tocopherol and tocotrienol isomers.

(From Abidi and Rennick, *J.*

Chromatogr. A, 913:379–386, 2001.

With permission.)

the development of cardiovascular disease, cancer, and dementia. Most of the attention on vitamin E has been focused on α -tocopherol; however, recent studies have pointed to the anti-inflammatory, antineoplastic, and natriuretic functions associated with γ -tocopherol (Hensley et al., 2004). Clermont et al. (2001) showed the use of vitamin E-coated dialyzer reduced oxidative stress in hemodialysis patients. Further work by Chao and coworkers (2002) found that supplementation of vitamins C and E dramatically improved the oxidation status in hemodialysis patients by decreasing the formation of lipid peroxides. The neuroprotective effect of vitamin E was demonstrated by Roghani and Behzadi (2001) by its ability to rapidly protect nigrostriatal dopaminergic neurons in an early model of Parkinson's disease in rat. Fariss and Zhang (2003) proposed that a chronic, high dose of vitamin E supplementation administered parenterally could provide an effective strategy for preventing or treating Parkinson's disease.

In addition to its role as an antioxidant, a number of nonantioxidant roles were highlighted for vitamin E by Azzi and Stocker (2000), including inhibition of protein kinase C and cell proliferation. Of the different vitamin E isomers, Osakada et al. (2004) recently found α -tocotrienol exhibited the most potent antiapoptotic neuroprotective effect on CNS neurons. These effects were attributed to its nonantioxidant

the efficacy of these vitamin E analogs as anticancer agents, including their recent, novel treatment of fatal human malignant mesothelioma and breast cancer (Tomasetti et al., 2004; Wang et al., 2005).

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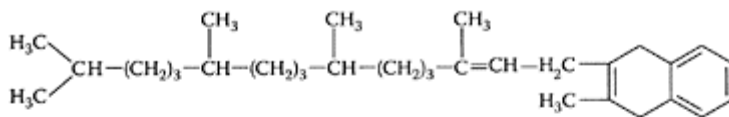
Vitamin K

see also Menadione Vitamin K is a family of fat-soluble vitamins with a number of important biological functions, including the formation of prothrombin and other blood-clotting factors. It is not a single compound but a group of quinones based on their source of origin. For example, phyloquinones (vitamin K₁) are found in plants, menaquinones (vitamin K₂) are synthesized by bacteria, while synthetic forms of vitamin K include menadione (K₃) (Scheme V.68). Leafy, green vegetables are good sources of vitamin K, which is also synthesized by bacteria in the small intestine. The presence of glutamic-acid residues in prothrombin (factor II) and other blood-clotting factors VII, IX, and X requires vitamin K for their carboxylation. This converts glutamic acid to γ -carboxyglutamic, enabling it to bind calcium, an essential step in the blood-clotting process (Furie and Furie, 1988, 1990).

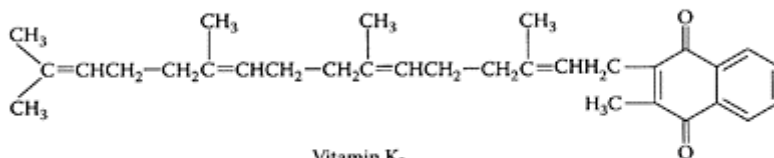
In addition to their important physiological role, vitamins K₁ and K₂ were also found to inhibit the growth of a hepatoma cell line Hep 3B (Wang et al., 1995). The low potency of the natural vitamins, however, led Wang et al. (1995) to synthesize 2-(2-

mercapto-ethanol)-3-methyl-1,4-napthoquinone, a vitamin K analog with 20 times the potency against Hep 3B cells. Inhibition of the induction of extracellular signal-regulated kinase (ERK) phosphorylation by this analog appeared to be one of the mechanisms involved in the apoptosis of rat hepatocytes (Wang et al., 2002). Ge et al. (2004) recently showed that mediation of c-Myc phosphorylation by this vitamin K analog resulted in enhancement of c-Myc protein degradation and reduced c-Myc protein levels, which may contribute to inhibition of the cell growth of human Hep 3B hepatoma lines.

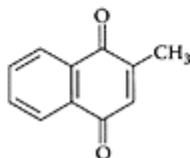
Vitamin K₃ or menadione (2-methyl-1,4-napthaquinone) has been used together with



Vitamin K₁



Vitamin K₂



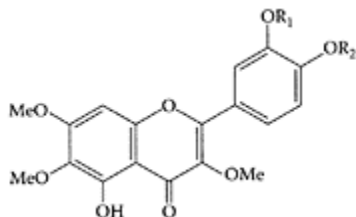
Vitamin K₃

SCHEME V.68 Structures of vitamins K₁ and K₂. (From Serfis and Katzenberger, *Colloids and Surfaces, A.. Physicochem. Eng. Aspects*, 138:91–95, 1998. With permission.)

chemotherapeutic agents to treat cancers (Tetef et al., 1995). More recent studies by McAmis et al. (2003) showed menadione caused oxidative stress and endothelial-cell cytotoxicity by altering intracellular thiols rather than increasing the amount of reactive-oxygen species (ROS). When vitamin C and vitamin K₃ were administered in a ratio of 100:1, synergistic antitumor activity was observed, in which the tumor cells were killed by a novel type of necrosis, autoshizis (Jamison et al., 2002). The latter is characterized by membrane damage and progressive loss of organelle-free cytoplasm.

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Compounds	R ₁	R ₂
2',3',5'-trihydroxy-3,6,7-trimethoxyflavone(Vx-1)	OH	OH
Vitexicarpin (Vx-5)	OH	OMe
Arternetin (Vx-6)	OMe	OMe

SCHEME V.69 Structural formulae of the polymethoxy-flavonoids isolated from *V. rotundifolia*. (From Ko et al., *Food Chem. Toxicol.*, 38:861–865, 2000. With permission.)

Vitex rotundifolia

Vitex rotundifolia or Beach vitex, is a plant native to the Pacific region with silvery-green, rounded leaves and purple flowers over the summer. During the winter, however, the plant remains dormant, producing berries. It has been traditionally used in Asia to treat colds, headaches, migraine, sore eyes, and myalgia (But et al., 1996). A polymethoxyflavonoid, vitexcarpin, was isolated from *V. rotundifolia* by You et al. (1998), which inhibited the proliferation of lymphocyte and the growth of some cancer cells.

Further work by Ko et al. (2000) isolated three polymethoxyflavonoids from the fruit of *V. rotundifolia*, which were characterized as 2',3',5'-trihydroxy-3,6,7 trimethoxyflavone (Vx-1), vitexicarpin (Vx-5), and artemetin (Vx-6) (Scheme V.69). These compounds all inhibited proliferation of human myeloid leukemia (HL-60) cells by inducing apoptosis.

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Vulgin

Ye and Ng (2001) identified an anti-fungal polypeptide from pinto beans with a molecular weight of 5 kDa and a sequence homology to cowpea. This polypeptide, subsequently referred to as vulgin, had an N-terminal sequence with some similarities to chitinases (Ye and Ng, 2003). These researchers also found vulgin inhibited HIV-1 reverse transcriptase activity, with an IC₅₀ of 58 mM.

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W

Walnuts

Walnuts, the seeds of *Juglans regia* L., have been used as a folk medicine in Europe and Asia for treating coughs and stomach ache (Perry, 1980) and cancer (Duke, 1989). Hu et al. (1998) showed that frequent consumption of nuts may offer some protection from coronary heart disease. Nuts, such as walnuts, are relatively high in polyunsaturated fatty acids, particularly omega-3 fatty acids. Iwamoto and coworkers (2000) examined the effect of walnuts on the serum cholesterol of Japanese men and women. A moderate intake of walnuts of 43–57 g/d, equivalent to 12.5 percent of energy, significantly reduced LDL cholesterol levels in both Japanese men and women by 0.18 mmol/L and 0.22 mmol/L, respectively. The ratio of LDL to HDL cholesterol was also significantly lowered, as was the apolipoprotein B concentration. A subsequent study by Almario et al. (2001) confirmed the ability of walnuts to beneficially reduce LDL cholesterol in patients with combined hyperlipidemia. Another study by Iwamoto et al. (2002) confirmed that a diet containing 44–58 g/day of walnuts fed to normal Japanese men and women lowered serum cholesterol, as well as had a beneficial effect on lipoproteins. In addition to lowering cholesterol, Ros and coworkers (2004) found that substituting walnuts for monounsaturated fat in a Mediterranean diet also improved endothelium vasodilation in hypercholesterolemic subjects. This suggested that the benefits of nuts went beyond just lowering cholesterol.

In addition to the oil, a polyphenolic-rich walnut extract containing ellagic acid, gallic acid, and flavonoids was shown by Anderson et al. (2001) to be a potent antioxidant by inhibiting oxidation of human plasma and LDL *in vitro*. The presence of ellagic acid suggested to Fukuda et al. (2003) the possible presence of tannins, such as ellagitannins. These researchers isolated a number of tannins from the butanol extract of walnut, including three hydrolyzable tannins, glansrins A-C, together with 13 known tannins. Glansrins A-C proved to be ellagitannins, with a tergalloyl or related poly-phenolic acyl group. Fukuda et al. (2003) demonstrated the antioxidant properties of these polyphenols by their SOD-like and radical-scavenging activities. A recent study by Kearny et al. (2004) showed that a diet enriched with 64 g/day of walnuts fed to hypercholesterolemic patients over six weeks significantly reduced total cholesterol (–5 percent) and LDL cholesterol (–9 percent). An additional trend observed was a 20 percent reduction in the large VLDL particle subclass. This study further demonstrated the cardiovascular health benefits of a daily diet enriched with walnuts.

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Wasabi (*Wasabia japonica*)

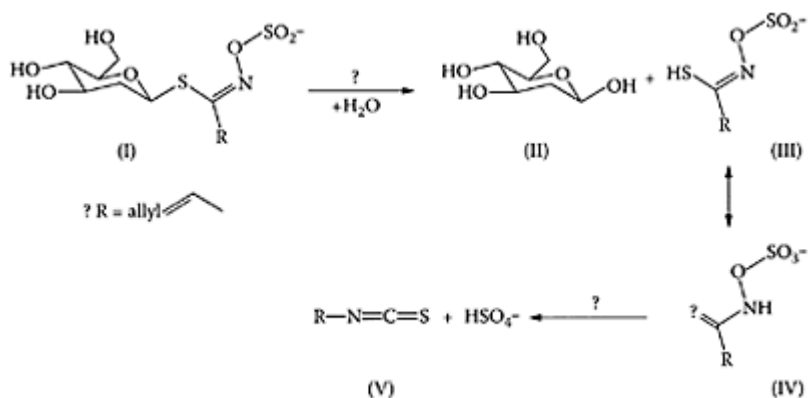
Wasabi, a member of the Japanese horseradish family with a number of important, health-related compounds, is usually served as a condiment with Japanese cuisine. Sinigrin was shown by Yu et al. (2001) to be the main, sulfur-containing species in wasabi initially hydrolyzed by myrosinase, followed by a nonenzymatic step, the Lossen rearrangement, to form isothiocyanates (Scheme W.70). Yano et al. (2000) showed isothiocyanate, 6-methylthiohexyl isothiocyanate (6MHITC), isolated from wasabi inhibited 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumorigenesis in mice, suppressing the initiation phase, that is the formation of O⁶-methylguanine (O⁶MG) (Figure W.99). O⁶MG is a promutagen adduct formed from activation of NNK via α -hydroxylation. 6MHIT significantly reduced the level of O⁶MG by 55 percent, very similar to the control containing phenylethyl isothiocyanate.

Morimitsu and coworkers (2000) isolated 6-methylsulfanylhexyl isothiocyanate from wasabi and showed it possessed antiplatelet and anticancer properties. Subsequent work by Watanabe et al. (2003) identified the active component in an ethanol extract capable of inducing apoptosis as 6-methylsulfanylhexyl isothiocyanate by its ability to inhibit the cell growth of human monoblastic leukemia U937 cells.

Shin et al. (2004) recently observed the bactericidal properties of wasabi against *Helicobacter pylori*. In addition to allyl isothiocyanate, several other components were also responsible for the effectiveness of wasabi.

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SCHEME W.70 Degradation of β -D-S-glucosides (I) by myrosinase (β -thioglucoside glucosylhydrolase) and related biochemistry. The initial hydrolysis of (I) yields glucose (II) and (III), which will be in equilibrium with (IV), is then thought to undergo a Lossen rearrangement to produce the isothiocyanate (V) and sulfate. (From Yu et al., *Biochim. Biophys. Acta*, 1527:156–160, 2001.)

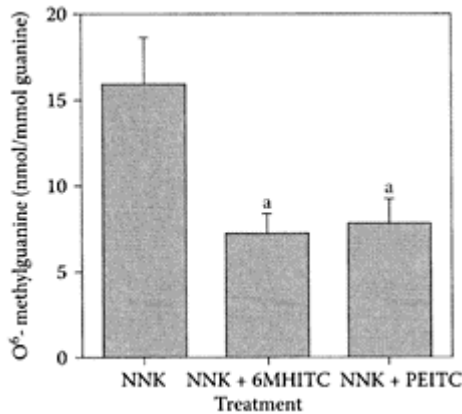


FIGURE W.99 The effect of 6MHITC treatment on pulmonary O⁶-methylguanine level in mice treated with NNK. Values are expressed as the mean \pm SE from five mice, (a) Significantly different from the NNK-treated group ($p < 0.05$). (From Yano et al., *Cancer Lett.*, 155:115–120, 2000. With permission.)

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Wheat bran

Wheat bran was shown to decrease the mucosal formation of aberrant crypt foci, an important marker for determining the efficacy of colon cancer preventative agents (Earnest et al., 1999). In fact, wheat bran was found to be the most effective fiber for protecting against colon cancer. Whether this was related to fermentation of the fiber and

the release of short-chain fatty acids, particularly butyric acid, a known inhibitor of tumor growth, remains unclear. Zile and coworkers (1998) also showed that inclusion of wheat bran suppressed mammary-gland tumorigenesis in experimental animals. Wheat dietary fiber comprises less than wheat bran, so that other nutrients besides dietary fiber may also protect against cancer. Such components were thought to be phenolic acids, lignans, and flavonoids (Ferguson and Harris, 1999). The effectiveness of different dietary components, wheat bran (WB), curcumin (CUR), rutin (RUT), and benzyl isothiocyanate (BIT), on the formation aberrant crypt foci (ACF), colorectal tumors, and selected gene expression in azoxymethane-treated F344 rats were compared by Wijnands et al. (2004). Of the different dietary components, only WB and CUR protected against colorectal cancer compared to RUT and BIT.

Wheat bran has also been associated with considerable antioxidant activity due to the concentration of phenolics in the bran portion of the grain (Zhou and Yu, 2004). Bran extracts of hard wheat varieties, Akron and Trego, grown at three different locations in Colorado, were shown by Yu et al. (2004) to significantly reduce lipid peroxidation in human LDL *in vitro*. They also found that the bran absorbed oxygen radicals, with the potential of preventing them from attacking biological molecules. Yuan et al. (2004) showed that the water-soluble feruloyl oligosaccharides in the insoluble dietary fiber of wheat bran scavenged 2,2-diphenyl-1-picrylhydrazine (DPPH) free radicals, as well as inhibited oxidative hemolysis of rat erythrocytes induced by 2,2-azobis-2-amidinopropane dihydrochloride (AAPH) by 91.7 percent.

Thus, incorporation of wheat-bran products may provide functional foods capable of preventing atherosclerosis and related diseases, as well as a new source of natural antioxidants.

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Wheat flour

Whole-wheat flour was reported by Adam and coworkers (2001) to lower plasma and hepatic lipids in rats. Since whole-wheat flour is normally consumed in a processed product, such as bread, Adams et al. (2003) showed breadmaking (fermentation, starch gelatinization, heating) had a hypolipidemic effect compared to native whole-wheat flour. Rats fed a semipurified diet containing 70 percent whole-wheat flour (WWF) or 70 percent desiccated whole-wheat bread (WWB) had significantly ($p<0.05$) lower plasma and liver

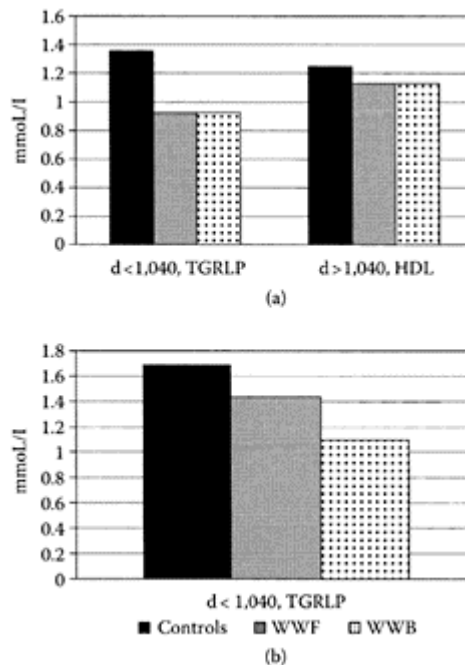


FIGURE W.100 Differences in the repartition of cholesterol (panel a) in plasma lipoprotein fractions of rats fed the control, WWF, and WWB diets. Each value is a mean of triplicate analyses of a pool of plasma. The fractions with a density of less than 1.040 kg/L corresponded to triacylglycerol-rich lipoproteins with a lower contribution of LDL. The

fractions with a density higher than 1.040 kg/L corresponded essentially to HDL. (From Adam et al., *Food Chem.*, 80:337–344, 2003. With permission.)

cholesterol levels compared to a control fiber-free starch diet. A closer examination of the plasma lipoproteins showed the triacylglycerol fraction (TGRLP, $d < 1.040$ kg/L) was 33 percent lower in animals fed WWF or WWB diets compared to the control, accounting for decreases of 14 percent and 24 percent, respectively. No differences were evident in the HDL fraction (Figure W.100). Total steroid excretion was significantly ($p < 0.01$) higher in the cereal diets, but was higher with the WWB diet. This corresponded to a reduction in cholesterol absorption of 26 percent for WWB compared to 38 percent and 52 percent for the WWF and control diets.

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Whey

see also α -Lactalbumin and Lactoferrin The whey fraction of bovine milk is rich source of immunomodulators, including the β -lactoglobulin, α -lactalbumin, lactoferrin, lactoperoxidase, and such tissue growth factors as TGF- β (Buonous et al., 1981; Stoeck et al., 1986; Dababbi et al., 1998; Wong et al., 1997, 1998). The unique immunomodulatory properties of a whey-protein concentrate (WPC) obtained from rennet casein whey was shown by Low et al. (2001) to markedly increase the intestinal-tract antibody responses in BALB/c mice over a 12-week period. Further research by Low and coworkers (2003) showed WPC increased humoral immune response in BALB/c mice immunized with such antigens as influenza virus, diphtheria, tetanus toxoids, poliomyelitis vaccine, ovalbumin, and cholera toxin subunit. The ability of dietary WPC to boost immune response in mice may be applicable for boosting postvaccination in humans, especially in children and the elderly with suboptimal immunity.

Tong et al. (2000) examined the antioxidant activity of a high-molecular-weight (HMW) fraction from whey. Using a salmon-oil emulsion, the antioxidant activity of the HMW fraction appeared dependent on the availability of sulfhydryl groups. However,

even when the sulfhydryl groups were blocked, whey proteins still exhibited significant antioxidant activity. This was attributed to the scavenging activity of other amino acids in whey proteins by the HMW fraction's ability to scavenge peroxy radicals generated by β -PE decay. An additional antioxidant mechanism of whey proteins was reported to be metal chelation.

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Wheat germ

A commercial wheat germ was enzymically hydrolyzed by Arrigoni et al. (2002) and then subjected to fermentation with fresh human feces under anaerobic conditions. The short-chain fatty acids produced were high in propionates, suggesting wheat germ behaved as a prebiotic by its support of bifidobacteria.

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Whole grains

see also **Wheat, Barley, Maize or Corn, Millet, Oats, Sorghum, and Triticale**
Epidemiological evidence supports an inverse relationship between consumption of cereal fiber or whole grains and type 2 diabetes (Meyer et al., 2000; Liu et al., 2000; Salmeron et al., 1997a, b), cardiovascular disease (Jacobs et al., 1998, 1999), and total mortality (Jacobs et al., 1998, 1999). Whole grains from cereals (wheat, rice, maize, oats, barley, triticale, sorghum, and millet) are rich in phytochemicals, such as dietary fiber, resistant starch, oligosaccharides, and phytoestrogens, some exhibiting anticarcinogenic activity (Slavin et al., 1999). Table W.63 summarizes the range of components and their health-related properties.

Phytoestrogens appear to play a role in reducing the risk of cardiovascular disease, diabetes, and some cancers. The regular consumption of whole grains significantly reduces the risk of coronary heart disease (Rimm et al., 1996; Jacobs et al., 1998; Liu et al., 1999). Jacobs and coworkers (2002) reported that whole-grain elevated serum enterolactone in hyperinsulinemic women. Previous studies showed that the risk of incidence of heart disease was reduced in Finnish men when serum enterolactone was in the upper quartile (Vanharanta et al., 1999). McKeown et al. (2002) reported that increased intake of whole grains had a favorable effect on the metabolic risk factors associated with cardiovascular disease and type 2 diabetes. Pereira and coworkers (2002) confirmed the improvement of insulin insensitivity in hyperinsulinemic and obese adults following the consumption of whole grains. A prospective study in men by Fung et al. (2002) also found that diets high in whole grains reduced the risk of type 2 diabetes and should replace refined grains.

TABLE W.63

Selected Components in Whole Grains and Their Postulated Mechanisms

Compo nents	Antio xidant	Tumor Growth Suppressor	Enzyme Mod ulator	Bin ding ???????	Che mical	Chole sterol- lowering	Gut Modifier	Horm onal Effects
Dietary fiber			✓			✓	✓	✓
Oligosaccharides			✓	✓		✓	✓	
Flavonoids	✓	✓	✓					
Inositols	✓							
Lignin	✓							
n-3 Fatty acids		✓				✓		
Phenolics	✓	✓	✓					
Phytates	✓							

Phytoestrogens	✓	✓		✓
Protease inhibitor		✓		
Saponins		✓		
Selenium	✓	✓		
Tocopherol	✓		✓	
Zinc	✓			✓

¹ Source: Adapted from Slavin et al. (1997) and Kohlmeier et al. (1995).

² Source: Taken from Slavin et al., *Am. J. Clin Nutr.* 70:459S-463S, 1999. With permission.

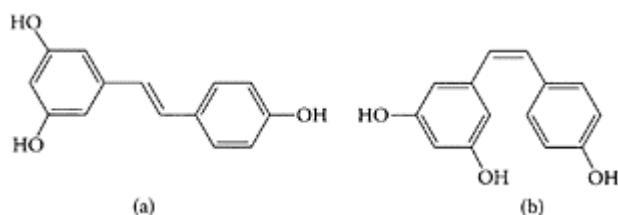
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Wine

see also Red wines and Resveratrol The relationship between wine and cardiovascular disease arose from the fact that in certain parts of France, where people consumed greater amounts of animal fats, the incidence of cardiovascular disease was remarkably low compared to North America. This phenomenon, referred to as the “French Paradox,” was subsequently attributed to the greater consumption of red wine. Frankel and coworkers (1993) showed it was the phenolics in wine that inhibited oxidation of human LDL cholesterol and, hence, the progression of atherosclerosis. This observation was confirmed by other researchers, including Tedesco et al. (2000), who demonstrated the beneficial effects of the nonalcoholic wine components, mainly polyphenols, in protecting red blood cells against oxidative stress. FernandezPachon et al. (2004) assessed the antioxidant activity of different wine samples and found it was higher in red wine compared to either white or sherry wines. Auger et al. (2001) showed a phenolic extract from red wine reduced atherosclerosis in hypercholesterolemic Golden Syrian hamsters. One of the major polyphenols found in red wine is resveratrol (3,5,4'-trihydroxystilbene) present as *trans* and *cis* isomers, depending on the type of wine (Scheme W.71). Most studies, however, have focused on the *trans* isomer and its antioxidant and antiproliferative activities *in vitro* (Briviba et al., 2002;



SCHEME W.71 Structure of the *trans*- (a) and *cis*- (b) isomers of resveratrol. (From Kolouchova-Hanzlikova et al., *Food Chem.*, 87:151–158, 2004. With permission.)

Olas and Wachowicz, 2002; Zoberi et al., 2002). Resveratrol also inhibits angiogenesis, the process of new blood-cell growth associated with tumor growth and metastasis (Cao et al., 2002).

Among the proposed mechanisms for the protective action of red wine is its effect on HDL metabolism (Gaziano et al., 1993; Lavy et al., 1994). HDL not only reverses cholesterol transport but also inhibits accumulation of lipid peroxides on LDL (Aviram et al., 1998a). Paraoxonase (PON), an enzyme on HDL particles, is responsible for the antioxidant properties of HDL by inhibiting or preventing oxidation of LDL and HDL. In addition, PON was thought to stimulate cholesterol efflux, the first step in reversing cholesterol transport (Aviram et al., 1998a, b; Mackness et al., 1993). Sarandol et al. (2004) examined the effect of wine consumption on the serum paraoxonase/ary-lesterase activities of PON, as well as lipoprotein oxidizability in 14 healthy males between the ages of 25 and 38 years. While there was no change in paraoxonase activity, there was a 22 percent decrease in arylesterase activity following wine consumption. However, the ability of red wine to protect lipoproteins from oxidation was clearly evident by the significant (29 percent) decrease in oxidation of apolipoprotein B-containing lipoproteins. Gomez-Cordoves et al. (2001) also showed wine phenolics could decrease melanogenic activity, suggesting their potential as therapeutic agents in the treatment of human melanoma.

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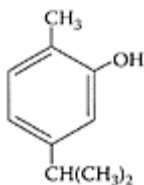
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Winter savory

Winter savory (*Satureja montana* L.), an aromatic and medicinal herb used as a folk remedy for many diseases, grows along the Adriatic coast and parts of Croatia. It contains a number of biologically active components including triterpenes, flavonoids, and rosmarinic acid (Escudero et al., 1985; ThomasBarberan et al., 1987; Reschke, 1983). Madsen et al. (1996) found extracts from a number of plants, including winter savory, were high in antioxidants. The broad-spectrum antimicrobial activity of the essential oil and ethanol extracts from winter savory was demonstrated in several studies, including its ability to control potential pathogenic and spoilage yeasts (Pepeljnak et al., 1999; Ciani et al., 2000).

The value of savory oil was attributed by Lawrence (1979) to its high carvacrol content and fresh, spicy phenolic notes reminiscent of oregano and thyme. Carvacrol was approved as a flavoring agent by the FDA and the Council of Europe at a level of 2 ppm in beverages, 5 ppm in food, and 25 ppm in candy (De Vincent et al., 2004). These researchers pointed out the need for long-term toxicological studies to establish its safety. Mastelic and Kerkovic



Carvacrol. (From De Vicenzi et al., *Fitoterapia*, 75:801–804, 2004. With permission.)

(2003) found a moderate correlation between the chemical composition of savory oil and its volatile aglycones. The compounds identified were thymol, p-cymene-9-ol, geraniol, 1-octen3-ol, carvacrol, and nerol.

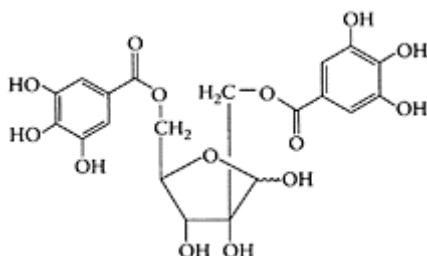
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Witch hazel

Witch hazel (*Hamamelis virginiana* L.), a deciduous shrub native to Eastern North America and Canada, has been used in skin-care products and for treating sunburn, irritated skin, and atopic eczema (Korting et al., 1995). One of the main components in the bark extract from witch hazel is hamamelitannin, a compound composed of two gallate moieties and the sugar hamamelose (Hartisch and Kolodzie, 1996).

Hamamelitannin was reported to protect cells from ultraviolet B radiation and to scavenge superoxide and hydroxyl radicals



Structure of hamamelitannin (2,5'-di-O-galloyl hamamelose). (Adapted from Dauer et al., *Phytochemistry*, 63:199–207, 2003.)

(Masaki et al., 1995a, b). *In vitro* studies by Habtermariam (2002) found hamamelitannin inhibited the activity of the tumor necrosis factor (α -TNF), preventing its cytotoxic induction of endothelial cell death. An important prerequisite of endothelial cell death is DNA fragmentation. Hamamelitannin prevented DNA fragmentation by α -TNF in a concentration-dependent manner, as shown in Figure W.101. However, it had no effect on TNF-induced upregulation of endothelial adhesiveness. In addition to tannins, Dauer et al. (2003) reported that catechin present in the bark of *Hamamelis virginiana* also protected human hepatoma cells (Hep G2) from benz(a)pyrene (BP) and (\pm)-anti-benz(a)pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE)-induced DNA damage by inactivation of the mutagen. These compounds may prevent genetic damage caused by genotoxins present in the diet or environment.

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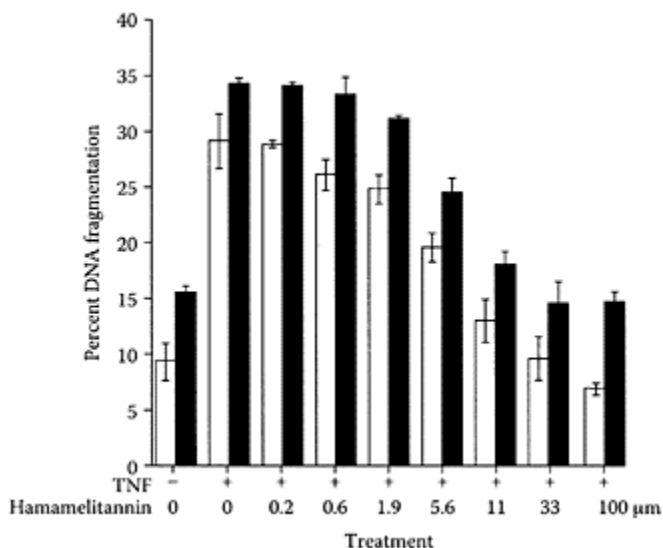


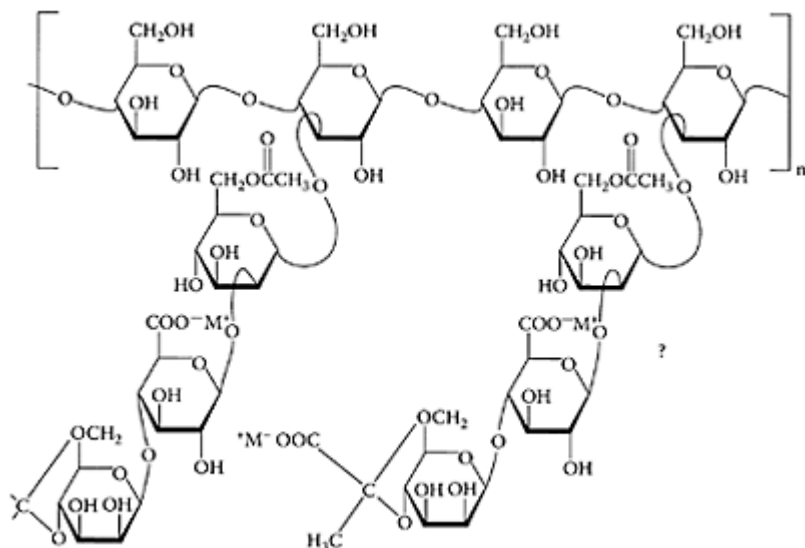
FIGURE W.101 Inhibition of TNF-mediated DNA fragmentation by hamamelitannin. Endothelial cells were treated with TNF and actinomycin D in the presence or absence of hamamelitannin. DNA leakage was assessed to the medium (open bars), and DNA fragmentation is quantified from cell lysates (solid bars). Results are mean values \pm SEM from four separate experiments. (From Habtemariam, *Toxicon.*, 40:83–88, 2003. With permission.)

X

Xanthan gum

Xanthan, an industrial microbial gum produced by aerobic fermentation of *Xanthomonas campestris*, consists of a β -(164)-D-glucopyranose glucan backbone with side chains composed of (163)- α -linked D-mannopyranose-(261)- β -D-glucuronic acid-(461) β -D-mannopyranose on alternate residues (Scheme X.72). The rheological properties of xanthan makes it an ideal emulsifier and thickener in foods, as well as in cosmetics and pharmaceuticals (Garcia-Ochoa et al., 2000). As a complex polysaccharide, it would be expected to have a low glycemic index. Sun and Griffiths (2000) reported that immobilization of *Bifidobacteria* on a novel, acid-stable bead made from gellan gum and xanthan gum significantly enhanced their tolerance to high-acid environments compared to the free cells when added to pasteurized yogurt and stored for five weeks at refrigerated temperatures. This technology could be useful for delivering probiotic cultures to the gastrointestinal tract of humans and animals.

Xanthan gum also has drug release-retarding properties, which are enhanced in the presence of galactomannan gums, such as guar gum (Melia, 1991). This property is important, as it permits the delivery of drugs to a particular site, which not only reduces the side effects of the drug but increases its pharmacological response. Sinha et al. (2004) prepared tablets of 50 mg fluoracil compression coated with a mixture of xanthan and guar gums. 5-Fluoracil, an established pyrimidine drug for treating colon cancer, inhibits RNA function and the processing and synthesis of thymidylate. The compressed tablet, coated with a xanthan gum: guar gum combination of 10:20, permitted 5-fluoracil to move down the upper part of the gastrointestinal tract without exposing it to its toxic side effects, releasing it specifically in the colon.



SCHEME X.72 Structure of xanthan gum. (From Garcia-Ochoa et al., *Biotechnol. Adv.*, 18:549–579, 2000. With permission.)

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Xanthophylls

see Carotenoids, Lutein, and Zeaxanthin Xanthophylls are oxygenated carotenoids found in plants. One of the richest sources is the marigold flower. Xanthophylls are important nutraceuticals, because they prevent cancer (Chew et al., 1996) and oxidation of cellular lipids (Zhang et al., 1991), as well as age-related macular degeneration

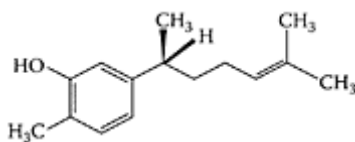
(Fullmer and Shao, 2001). The two most important xanthophylls are lutein and zeaxanthin.

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Xanthorrhizol

Xanthorrhizol, a sesquiterpenoid compound, is one of the major constituents in the rhizome of *Curcuma* species. Hwang and coworkers (2000) found that Xanthorrhizol had the highest antibacterial activity against *Streptococcus* species responsible for dental caries.



Structure of Xanthorrhizol. (From Choi et al., *Biochem. Biophys. Res. Commun.*, 326:210–217, 2005. With permission.)

Xanthorrhizol has been used as a folk medicine for treating rheumatic and stomach ailments. Lee et al. (2002) showed Xanthorrhizol suppressed COX-2 and iNOS activities in mouse macrophage cells, while Kim et al. (2004) reported it attenuated induction of COX-2 and iNOS genes in cisplatin-induced hepatotoxicity in mouse-macrophage cells. Cisplatin, a widely used cancer drug, suffers from serious side effects, such as nephrotoxicity. The prevention of hepatotoxicity and nephrotoxicity induced by high doses of cisplatin could be alleviated by combining it with Xanthorrhizol. This combination could enhance the safety of cisplatin in cancer therapy. Using an experimental mouse-lung metastasis model, Choi et al. (2004) reported Xanthorrhizol exerted its antimetastatic properties *in vivo* through the possible expression of COX-2 and the activity of MM-9.

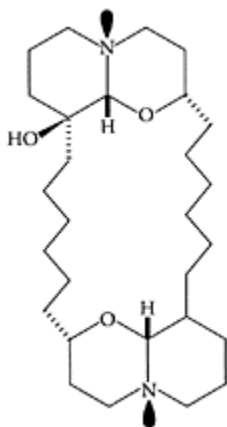
Campos et al. (2000) observed that Xanthorrhizol, isolated from the dried roots of *Iostephane heterophylla*, relaxed smooth-muscle cells in the rat aorta previously contracted with high-KCl, CaCl₂, or noradrenaline. This was the first report of a vasorelaxant bioactive compound from the Cachani complex of medicinal plants.

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Xestospongins

Xestospongins, a group of macrocyclic *bis*-1-oxaquinolizidines isolated from the Australian sponge *Xestospongi* species, are potent blockers of inositol 1,4,5-triphosphate (IP₃)-induced Ca²⁺ mobilization in cerebellar and intact cells (Gafni et al., 1997). They proved valuable tools for studying the molecular pharmacology of the myo-inositol 1,4,5-triphosphate receptor in intact-cell preparations. The most potent antagonist of myo-inositol IP₃ proved to be xestospongins C. The vasodilatory properties of xestospongins were first recognized more than 20 years ago by Nakagawa et al. (1984). Subsequent research has rationalized these properties to xestospongins' IP₃ receptor-blocking activity within the vasculature. Xestospongins C was suggested by Dassen et al. (2003) as a possible new therapy for



Xestospongine C. (From Wilcox et al., *TiPS*, 19:467–475, 1998. With permission.)

treating Detrusor overactivity (DO). DO is a condition defined as the presence of involuntary detrusor (the main bladder muscle) contractions leading to urinary incontinence. Dassen et al. (2003) found that the ability of xestospongine C to inhibit IP₃ pathway reduced spontaneous detrusor contractions. Kajioka et al. (2005), however, reported there were two mechanisms, an IP₃-dependent and an IP₃-independent, responsible for the phasic and tonic contractions of the urinary bladder associated with DO.

Wilcox et al. (1998) suggested that the anti-hypertensive potential should lead to the synthesis and pharmacological assessment of analogs of xestospongins. Rao and coworkers (1998) examined a number of marine biomolecules on rat brain nitric-oxide synthase (NOS) activity. Nitric oxide mediates a variety of physiological functions and is considered a messenger molecule. Xestospongine D proved to be one of only two compounds that significantly inhibited NOS activity, which might explain its toxicity due to impairment in neurotransmission.

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Xylooligosaccharides

Xylooligosaccharides, sugar oligomers composed of xylose units, are found naturally in bamboo shoots, fruits, vegetables, milk, and honey. They are utilized in Pharmaceuticals, feed formulations, for agricultural purposes, and in foods (Vazquez, 2001). Xylooligosaccharides are extremely stable over a wide pH range (2.5–8.0) compared to the nondigestible fructooligosaccharides.

The primary health properties of Xylooligosaccharides are related to their effect on the gastrointestinal flora. Xylooligosaccharides enhance the growth of *Bifidobacterium* spp. in the gastrointestinal tract (Suwa et al., 1999), as well as increases the production of short-chain fatty acids in the rat caecum (Campbell et al., 1997; Imaizumi et al., 1991). As prebiotics, they stimulate *Bifidobacterium* in the gastrointestinal tract, which provides a number of important health benefits.

Ando et al. (2004) published the first report on the effect of bamboo Xylooligosaccharides on the viability of leukemia cells. Several hot-compressed, water-fractionated bamboo products were separated, including Fraction A. This fraction, composed of xylose, Xylooligosaccharides, and water-soluble lignin, markedly reduced the viability of leukemia-cell lines derived from acute lymphoblastic leukemia (ALL), Jurkat, and MOLT-4. Induction of apoptosis induced by Fraction A on ALL-derived cells was attributed to Xylooligosaccharides. However, the cytotoxicity of the hot-compressed, water-fractionated bamboo products were less than that observed for other natural products, such as lectins.

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Y

Yarrow

Yarrow (*Achillea millefolium*) is a perennial plant native to Europe and Asia, with a number of species growing in temperate North America (Konemann, 1999). It has been used in folk medicine as an appetizer, wound healer, diuretic, carminative, or menstrual regulator (Botys, 1999). Yarrow contains flavonoids, alkaloids, triterpenes, coumarins, and tannins, as well as sesquiterpene lactones. Tozyo et al. (1994) identified three sesquiterpenes in yarrow, achimillic acids A, B, and C, all of which acted as antitumor agents against mouse P-388 leukemia cells *in vivo*. An earlier study by ZitterlEglseer et al. (1992) reported the presence of rupicolin and 11, 13-dehydrodeacetyl-matricarin in yarrow, both of which had anti-inflammatory activity.

Candan et al. (2003) evaluated the antioxidant and antimicrobial properties in the essential oil and methanolic extract of *Achillea millefolium* sub. *Millefolium* (*Asteracea*). Of 36 compounds identified in the essential oil, eucalyptol, camphor, α -terpineol, β -pinene, and borneol accounted for 60.7 percent of the oil. The oil had moderate antimicrobial activity against a number of organisms, including *Staphylococcus pneumonia*, *Clostridium perfringens*, and *Candida albicans*. The antimicrobial properties were attributed, in part, to the presence of eucalyptol (1,8-cineole), camphor, and borneol (Pattnaik et al., 1997; Tzakou et al., 2001; Tabanca et al., 2001).

Montanari and coworkers (1998) monitored the morphological changes in the germinal epithelium of Swiss mice treated with ethanolic and hydroalcoholic extracts of *A. millefolium* flowers. The antispermatogenic action of *A. millefolium* suggested it might be used as an antifertility agent. Dalsenter et al. (2004) pointed out the need for long-term animal reproductive and toxicological studies and that further studies were needed to determine the real risk to humans.

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Yellow mustard (*Sinapis alba*)

“White” or “yellow” mustard is grown extensively in western Canada for use as a condiment (Cui and Eskin, 1998). Of the two principal species grown, oriental and yellow mustard, yellow mustard contains less oil but is much richer in mucilage. A detailed examination of yellow-mustard gum identified a unique water-soluble 1,4 linked β -glucose with ethyl and propyl groups randomly distributed at the C2, 3, and 6 positions (Cui et al., 1993). Yellow-mustard gum is the only natural gum that resembles xanthan gum by exhibiting shear, thinning behavior at low concentrations, forming weak-gel structures and interacting synergistically with galactomannans (Cui et al., 2005).

Since yellow-mustard gum is a dietary fiber, it would be expected to regularize colonic function, normalize serum lipids, and attenuate postprandial glucose response and possibly suppress appetite. Begin et al. (1988) showed yellow-mustard gum, guar gum, oat β -glucan, and carboxymethylcellulose all significantly decreased postprandial insulin levels by slowing glucose absorption. In addition, yellow-mustard gum decreased insulemia by delaying gastric emptying. Incorporating yellow-mustard fiber into white bread at levels not affecting palatability showed a modest but significant reduction in the glycemic index on the bread in normal and diabetic volunteers (Jenkins et al., 1987).

The anticancer potential of yellow mustard was recently demonstrated by Eskin and Bird (unpublished data) in male Sprague-Dawley rats injected with the specific colon carcinogen, azoxymethane (AOM). Animals were maintained on a diet with or without 5 percent yellow-mustard gum over a six-week period. A significant ($p < 0.05$) decrease in the number of advanced aberrant crypt foci (ACF > 7 crypts) was observed in the yellow-mustard-fed rats, which accounted for a reduction of more than 90 percent. Further work is under way to explore the anticancer properties of yellow-mustard gum.

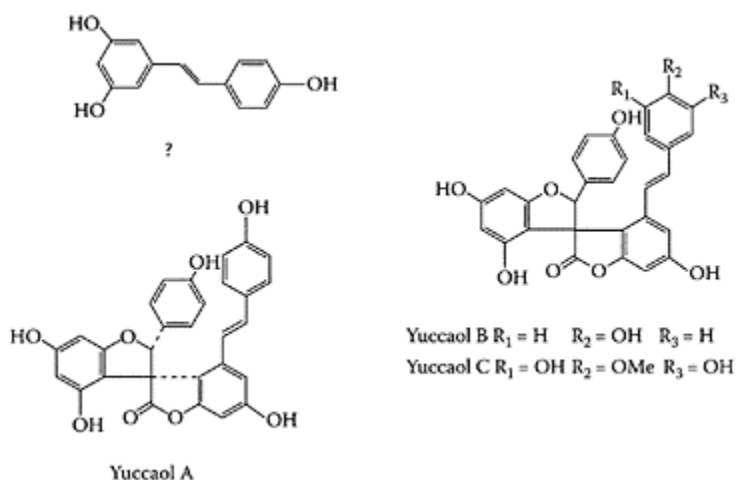
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Yucca

Yucca species (*Agavaceae*) are found growing in arid areas. Of these, *Yucca periculosa*, F.Baker, known as palmitos or izote, is a tree found in semiarid regions of Mexico. Torres and coworkers (2003) isolated stilbenes from the bark of *Yucca periculosa*, such as in the Tehuacan-Cuicatlan Valley, with only a few being of medicinal interest. Of the various *Yucca* species, *Y. schidigera* had the highest saponin content (Oleszek et al., 2001a), with its condensed juice widely used as food, cosmetic, and pharmaceutical additives (Cheeke, 1998). *Y. schidigera*, a folk medicine by American Indians and early settlers, has GRAS (generally regarded as safe) status by the FDA for human use. A number of phenolic compounds have been identified in the methanolic extract from the bark of *Y. schidigera*, including yuccaol A-C, a C15 unit derived from a flavonoid skeleton and a stilbenic portion, closely related to resveratrol (Scheme Y.73) (Oleszek et al., 2001b).

Tsai et al. (1999) showed resveratrol strongly inhibited the production of nitric oxide (NO) in activated macrophages, as well as downregulated the cytosolic inducible isoform of nitric-oxide synthase (iNOS), a key mediator in inflammatory processes. Subsequent research by Olas and coworkers (2002) reported yuccaol A-C exhibited antiplatelet activity. Recent research by Marzocco et al. (2004) showed yuccaol C inhibited iNOS protein



SCHEME Y.73 Chemical structures of *Yucca schidigera*-derived yucaol A–C and resveratrol. (From Marzocco et al., *Life Sci.*, 75:1491–1501, 2004. With permission.)

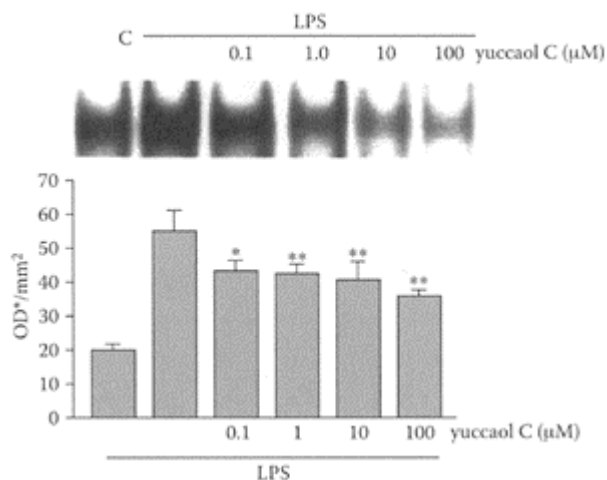


FIGURE Y.102 Effect of yuccaol C (0.1–100 mM) on NF- κ B activation in LPS-stimulated J774.A1 macrophages. Values, mean \pm S.E.M. are expressed as optical density/mm² of at least three independent experiments with three

replicates each. Comparisons were performed using one-way ANOVA test. * $p < 0.05$ and ** $p < 0.01$. (From Marzocco et al., *Life Sci.*, 75:1491–1501, 2004. With permission.)

expression, preventing activation of NF- κ B (Figure Y.102). Induction of specific NF- κ B binding activity by LPS was significantly reduced by yuccaol C (0.1–100 mM) added to cells 1 h prior to LPS challenge. Yuccaol A had no effect on NF- κ B expression. The ability of yuccaol to prevent NF- κ B activation suggests that, together with resveratrol, it could be used to control the inflammatory process.

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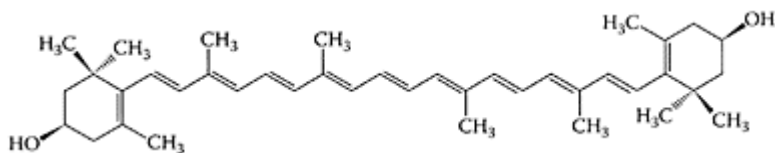
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Z

Zeaxanthin

Zeaxanthin, a hydroxylated carotenoid, is an important plant food xanthophyll. Together with lutein, they are found in the macula pigment of the central retina of the eye responsible for the yellow coloration (Snodderly et al., 1986). Since the source of the macular pigment is solely dietary-based, studies have examined the possible relationship between the pigment and dietary intake. The majority of dietary zeaxanthin and lutein (78 percent) are obtained from such vegetables as spinach and orange pepper, although they are also found in egg yolk (Summerburg et al., 1998; USDA, 1998). The importance of the macula pigment is its protection against age-related maculopathy, one of the major causes of blindness in Western countries (Klaver et al., 1998). Modified diets that are supplemented with zeaxanthin and lutein were shown to augment or enhance the macular pigment optical density (Hammond et al., 1997; Johnson et al., 2000). Both zeaxanthin and lutein are strong antioxidants, as age-related maculopathy is due to a combination of cumulative blue-light damage or oxidative stress (Beatty et al., 2000). Thus, oxidative stress appears to play a role in such neurodegenerative diseases as age-related macular degeneration (ARMD), the primary cause of blindness in seniors in developed countries (Leibowitz et al., 1980; Klein et al., 1992).

Wrona and coworkers (2004) examined the ability of zeaxanthin to protect the outer layer of the retina containing photoreceptor outer segments and retinal pigment epithelium (RPE), possible targets of oxidative damage. Using ARPE 19 cells from the globes of a 19-year-old male donor, they showed that zeaxanthin, in the presence of ascorbic acid and α -tocopherol, significantly enhanced resistance to photo-induced oxidative stress. Compared to cells without added antioxidants, these cells had enhanced cell viability and accumulated fewer lipid hydroperoxides. A synergism was evident between zeaxanthin and vitamin E or C, which could play a role in protecting the cell membranes from oxidative damage. The reduction in the decay of zeaxanthin in the presence of either vitamin C or E, following photo-sensitized oxidation of ARPE-19 cells, pointed to their protective effects. The synergism between these antioxidants was responsible for preventing the depletion of zeaxanthin by free-radical degradation and repair of the semioxidized zeaxanthin molecules. Chen et al. (2005) recently reported the successful use of high-speed, counter-current chromatography for isolating and purifying zeaxanthin from the microalga *Microcystis aeruginosa*. For a further review of the relationship between serum and dietary levels of zeaxanthin, lutein, and macular pigment optical density, the article by Beatty et al. (2004) is recommended.



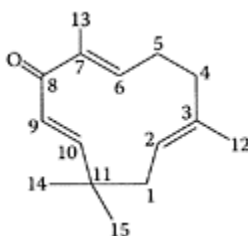
Zeaxanthin. (From Chen et al., *J. Chromatogr. A*, 1064:183–186, 2005. With permission.)

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Zerumbone

Zerumbone is a sesquiterpene obtained from a Southeast Asian edible ginger plant, *Zingiber zerumbet* Smith. The rhizomes of this plant were used for antiinflammation (Farnsworth and Bunyapraphatasara, 1992) while the young shoots and inflorescence were used in condiments (Jacquat and Bertossa, 1990). Murakami et al. (1999) first reported that the rhizomes of *Zingiber zerumbet* suppressed the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus activation in Raji cells. Further work by Murakami et al. (2002) showed that zerumbone suppressed carcinogenesis in a number of different models, including TPA-induced superoxide anion generation from both NADPH oxidase in dimethylsulfoxide-differentiated HL-60



Zerumbone. (From Tanaka et al., *Life Sci.*, 69:1935–1945, 2001. With permission.)

human acute promyelocytic leukemia cells and xanthine oxidase in AS52 Chinese hamster ovary cells. Zerumbone also induced apoptosis in human colonic adenocarcinoma cell lines. A structural analog of zerumbone, α -humulene, which lacked the $\alpha\beta$ -unsaturated carbonyl group in zerumbone, points to the importance of this group in the anti-inflammatory and chemopreventive properties of this nutraceutical.

Tanaka et al. (2001) showed dietary zerumbone reduced the development of colon cancer in male F344 rats injected with azoxymethane (AOM). Their results in Table Z.64 show a significant reduction in aberrant crypt foci (ACF) when fed 0.05 percent zerumbone. Of particular importance is the significant reduction in the number of large ACF from 11.1 in the control group to 2.3 and 0.7 in animals fed 0.01 and 0.05 percent zerumbone. Thus, zerumbone appeared to have strong chemopreventive properties,

TABLE Z.64

Incidence of Aberrant Crypt Foci (ACF) in Rats Treated with AOM and/or Zerumbone

Group no.	Treatment		Total no. of ACF/Colon	No. of Aberrant Crypts/Focus	No. of Large ACF (More than 4 Crypts/Focus)
	AOM	Zerumbone in diet (w/w)			
1	+	—	84±13 ^a	2.0±0.2	11.1±2.6
2	+	0.01%	72±17	1.6±0.2 ^b	2.3±1.4 ^c
3	+	0.05%	45±18 ^c	1.5±0.1	0.7±0.5 ^c

Note: Analysis of ACF was done in 8 rats each of groups 1–3 and 4 rats each of groups 4 and 5. There were no ACF in rats of groups 4 and 5.

^a Mean ± SD. ^{b,c} Significantly different vs. group 1 (^b*p* < 0.05, and ^c*p* < 0.001).

Source: Tanaka et al., *Life Sci.*, 69:1935–1945, 2001. With permission.

resulting from the suppression of COX-2 expression and proliferation of colonic mucosa and induction of phase II detoxification enzymes.

Further work by Nakamura et al. (2004) on the potential of zerumbone as a promising chemopreventive agent against colon and skin cancer confirmed its ability to reduce oxidative stress by inducing endogenous antioxidants, such as phase II enzymes.

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Zingiber officinale

see **Ginger**

Zucchini

see **Bryonolic acid**